

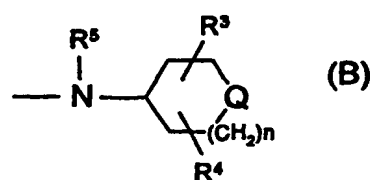
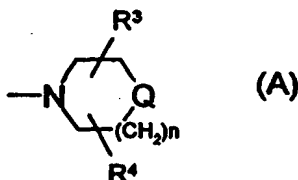
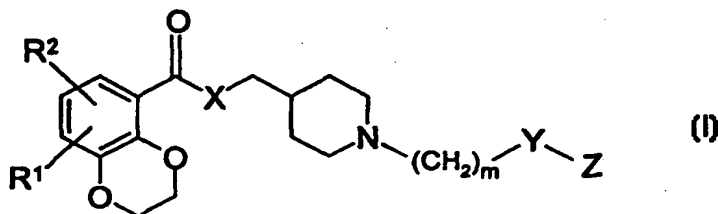


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 405/14, 413/14, A61K 31/445, 31/495, 31/35	A1	(11) International Publication Number: WO 00/15636 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/EP99/06402 (22) International Filing Date: 1 September 1999 (01.09.99) (30) Priority Data: 60/099,740 10 September 1998 (10.09.98) US 60/138,468 10 June 1999 (10.06.99) US (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Gren- zacherstrasse 124, CH-4070 Basle (CH). (72) Inventors: CLARK, Robin, Douglas; 2025 Columbia Street, Palo Alto, CA 94306 (US). JAHANGIR, Alam; 1622 Briarpoint Drive, San Jose, CA 95131 (US). (74) Agent: POPPE, Regina; Grenzacherstrasse 124, CH-4070 Basle (CH).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	

(54) Title: DIHYDROBENZODIOXINE CARBOXAMIDE AND KETONE DERIVATIVES AS 5-HT₄ RECEPTOR ANTAGONISTS**(57) Abstract**

This invention relates to certain 5-HT₄ receptor antagonist compounds represented by Formula (I), wherein Z is represented by formula (A) or (B), wherein R¹, R², R³, R⁴ and R⁵ and the other substituents are as defined in the specification; and the individual isomers, racemic or non-racemic mixtures of isomers, and pharmaceutically acceptable salts or hydrates thereof. The invention further relates to pharmaceutical compositions containing such compounds and for their use as therapeutic agents.



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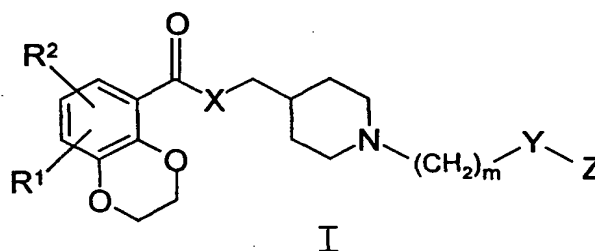
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DIHYDROBENZODIOXINE CARBOXAMIDE AND KETONE DERIVATIVES AS 5-HT₄ RECEPTOR ANTAGONISTS

This invention relates to compounds of formula



wherein:

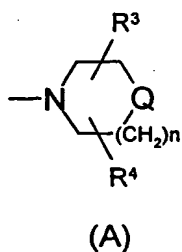
- 5 R¹ and R² are each independently in each occurrence hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halogen, amino or hydroxy;

X is -NH or -CH₂;

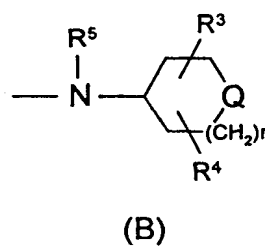
m is 2, 3, or 4;

Y is -SO₂;

- 10 Z is represented by formula (A) or (B):



or



wherein:

R³, R⁴, and R⁵ are each independently in each occurrence hydrogen or (C₁-C₆)alkyl;

- 15 Q is O, S, -NR⁶, or -CR⁷R⁸;

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n is 1 or 2;

wherein:

5 R^6 is hydrogen, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, heterocyclyl, heteroaryl, $-COR^9$, $-SO_2R^9$, $-CONR^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, or aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl;

R^7 is hydrogen or (C_1-C_6) alkyl;

R^8 is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, aryloxy, $-(CH_2)_pCONR^{10}R^{11}$, $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^7COR^9$, or $-(CH_2)_pNR^7SO_2R^9$; or

10 R^7 and R^8 taken together with the common ring carbon to which they are attached form a monocyclic saturated 5- or 6-membered ring optionally independently containing 0 or 1 heteroatom of nitrogen, oxygen, or sulfur;

wherein:

p is 0, 1, 2, 3 or 4;

15 R^9 is (C_1-C_6) alkyl, heteroaryl, heterocyclyl, or aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl; and

R^{10} and R^{11} are each independently hydrogen or (C_1-C_6) alkyl;

or individual isomers, racemic or non-racemic mixture of isomers, or pharmaceutically acceptable salts or hydrates thereof.

20 It has been shown that compounds of formula I are 5-HT₄ receptor antagonists.

5-HT (5-hydroxy-tryptamine), also referred to as serotonin, is a neurotransmitter with mixed and complex pharmacological characteristics and was first discovered in 1948. Serotonin acts both centrally and peripherally on discrete 5-HT
25 receptors. The 5-HT receptor family is presently delineated into seven major subclassifications, 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇, each of which may also be heterogeneous.

The 5-HT₄ receptors are widely distributed throughout the body and have various functions. For example, the 5-HT₄ receptors located on postganglionic parasympathetic autonomic efferent neurons of the urinary bladder mediate facilitation of neurogenic bladder detrusor contractions (see Ford, A.P.D.W. and Kava, M.S., *5-HT₄ Receptors in the Brain and Periphery*; Eglen, R.M., Ed., Springer-Verlag Berlin and R.G. Landes Company Georgetown, TX, 1998, pp 171-193; Waikar, M.V. *et al.*, *Br. J. Pharmacol.* 1994, 111, 213-218; Corsi, M. *et al.*, *Br. J. Pharmacol.* 1991, 104, 719-725). In the central nervous system, the 5-HT₄ receptors are found on neurons of the superior and inferior colliculi and in the hippocampus, and are thought to be involved in areas of the central nervous system affecting anxiety, depression, cognition, dependency, schizophrenia, appetite, thermoregulation, and such. In the gastrointestinal tract, the 5-HT₄ receptors are found on neurons, *e.g.*, myenteric plexus, as well as on smooth muscle and secretory cells, and appear to modulate gastrointestinal motility, evoke secretion in the alimentary tract, and stimulate cholinergic excitatory pathways involved in the peristaltic reflex (see Hegde, S.S., *5-HT₄ Receptors in the Brain and Periphery*; Eglen, R.M., Ed., Springer-Verlag Berlin and R.G. Landes Company Georgetown, TX, 1998, pp 150-169). In the cardiovascular system, the 5-HT₄ receptors mediate 5-HT induced positive inotropy and chronotropy in atrial myocytes, *e.g.*, bradyarrhythmia or tachyarrhythmia (see Kaumann, A. *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1991, 344, 150-159).

Thus, it is clear that 5-HT₄ receptor antagonists will offer distinct therapeutic advantages collectively in efficacy and rapidity of onset, particularly in urinary tract disorders related to autonomic mediation of storage and voiding reflexes. Additionally, because the 5-HT₄ receptors found in other organs, *e.g.*, the heart or gastrointestinal tract, are not essential for basic physiological function, minimal side effects are anticipated with improved tolerability (see Ford, A.P.D.W. and Kava, M.S., *supra*).

U.S. Patent No. 5,852,014 and PCT Published Application WO 93/18036 (Gaster *et al.*) refer to certain condensed indole carboxamide derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

U.S. Patent No. 5,763,458 (Clark *et al.*) and European Patent EP 0 700 383 B1 refer to certain dihydrobenzodioxine-propan-1-one derivatives which are disclosed as 5-HT₄ ligands.

5 U.S. Patent Nos. 5,741,801 and 5,872,134, and PCT Published Application WO 94/27987 (King *et al.*) refer to certain dihydrobenzodioxine-propan-1-one derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular or CNS disorders.

10 U.S. Patent No. 5,708,174 and PCT Published Application WO 94/08994 (King *et al.*) refer to certain heterocyclic carboxylate derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

15 U.S. Patent No. 5,705,509 and PCT Published Application WO 94/17071 (Gaster *et al.*) refer to certain heterocyclic carboxylate derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

U.S. Patent No. 5,705,498 and PCT Published Application WO 94/10174 (Gaster *et al.*) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as being useful in manufacturing medicaments for 5-HT₄ receptor antagonists.

20 U.S. Patent Nos. 5,654,320 and 5,798,367 (Catlow *et al.*) refer to certain indazole carboxamide derivatives which are disclosed as having 5-HT₄ receptor partial agonist and antagonist activity.

25 U.S. Patent Nos. 5,620,992 and 5,786,372, and PCT Published Application WO 94/05654 (King *et al.*) refer to certain dihydrobenzodioxine carboxylate derivatives which are disclosed as having 5-HT₄ receptor antagonist activity.

U.S. Patent No. 5,580,885 and PCT Published Application WO 93/05038 (King *et al.*) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as having 5-HT₄ receptor antagonist activity.

30 U.S. Patent Nos. 5,374,637, 5,521,314, 5,536,733, 5,552,553, 5,554,772, 5,565,582, 5,576,448, 5,602,129, 5,610,157, 5,616,583, 5,616,738, and 5,739,134,

and European Patent EP 0 389 037 B1, (Van Daele *et al.*) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as having gastrointestinal motility stimulating properties.

5 U.S. Patent Nos. 5,185,335 and 5,262,418 (Van Daele *et al.*) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as having gastrointestinal motility stimulating properties.

PCT Published Application WO 98/27058 (Bromidge *et al.*) refers to certain benzamide derivatives which are disclosed as having 5-HT₆ receptor activity.

10 PCT Published Application. WO 96/05166 (assigned to Yamanouchi) refers to certain heterocyclic-substituted alkyl-heterocycloalkylamine derivatives which are disclosed as having 5-HT₄ receptor agonist activity useful for treating CNS disorders and digestive tract movement.

15 PCT Published Application WO 94/29298 (Gaster *et al.*) refer to certain dihydrobenzodioxine carboxylate derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

20 PCT Published Application WO 94/08995 (Gaster *et al.*) refers to certain heterocyclic carboxamide derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

25 PCT Published Application WO 93/16072 (King *et al.*) refers to certain heterocyclic carboxamide derivatives which are disclosed as having 5-HT₄ receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

PCT Published Application WO 93/03725 (King *et al.*) refers to certain heterocyclic carboxamide derivatives which are disclosed as having 5-HT₄ receptor antagonist activity.

30 Japanese Patent Application JP 11001472 (assigned to Dainippon Pharm) refers to certain benzamide derivatives which are disclosed as having 5-HT₄

receptor antagonist activity useful for the prevention and treatment of digestive disorders.

Japanese Patent Application JP 9241241 (assigned to Morishita Roussel) refers to certain N-(1-substituted-4-piperidyl)benzamide derivatives which are disclosed as being selective 5-HT₄ receptor inhibitors useful for treating chronic gastritis, CNS disorders and urological diseases.

Clark, R.D., *5-HT₄ Receptors in the Brain and Periphery*, Eglen, R.M., Ed., Springer-Verlag Berlin and R.G. Landes Company Georgetown, TX, 1998, pp 1-48, refers to the medicinal chemistry of certain 5-HT₄ receptor ligands.

Clark, R.D. *et al.*, *Bioorganic & Medicinal Chem. Letters*. 1995, 5(18), 2119-2122, refers to certain benzodioxanyl ketone derivatives having 5-HT₄ receptor antagonist activity.

Clark, R.D. *et al.*, *Bioorganic & Medicinal Chem. Letters*. 1994, 4(20) 2477-2480, refers to certain benzoate derivatives having 5-HT₄ partial agonist activity.

Objects of the present invention are novel compounds of formula I, their isomers, racemic or non-racemic mixtures of isomers or pharmaceutically acceptable salts or hydrates thereof, the use in the treatment or prophylaxis of diseases, caused by 5-HT₄ receptors, the use of these compounds for manufacture of corresponding medicaments, processes for the manufacture of these novel compounds and medicaments, containing them. In detail, this invention relates to pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula I, or individual isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or hydrates thereof, in admixture with one or more suitable carriers. In a preferred embodiment, the pharmaceutical compositions are suitable for administration to a subject having a disease state that is alleviated by treatment with a 5-HT₄ receptor antagonist.

In a preferred embodiment, this invention relates to the use in the treatment of urinary tract disorder. Such as overactive bladder, outlet obstruction, outlet insufficiency, or pelvic hypersensitivity; most preferably overactive bladder.

This invention further relates to the use in the treatment of central nervous system (CNS) disorders or gastrointestinal disorders or cardiovascular disorders.

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

“Alkyl” means a monovalent branched or unbranched saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from one to twenty carbon atoms inclusive, unless otherwise indicated. Examples of an alkyl radical include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, n-hexyl, octyl, dodecyl, tetradecyl, eicosyl, and the like. Particular values of (C₁-C₆)alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, n-hexyl.

“Cycloalkyl” means a monovalent saturated carbocyclic radical consisting of one or more rings, which can optionally be substituted with hydroxy, cyano, alkyl, alkoxy, thioalkyl, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, and/or trifluoromethyl, unless otherwise indicated. Examples of cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, 3-ethylcyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Particular values of (C₃-C₈)cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

“Alkoxy” means a radical -OR wherein R is alkyl as defined above. Examples of an alkoxy radical include, but are not limited to, methoxy, ethoxy, isopropoxy, *sec*-butoxy, isobutoxy, and the like. Particular values of (C₁-C₆)alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *tert*-butoxy, pentoxy, isopentoxy, and hexoxy.

“Aryl” means the monovalent monocyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, which can optionally be substituted with hydroxy, cyano, lower alkyl, lower alkoxy, thioalkyl, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, and/or trifluoromethyl, unless otherwise indicated. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, biphenyl, indanyl, anthraquinolyl, and the like. A particularly preferred aryl includes phenyl.

"Aryloxy" means a radical -OR wherein R is an aryl radical as defined above. Examples of an aryloxy radical include, but are not limited to, phenoxy and the like.

5 "Heteroaryl" means the monovalent aromatic carbocyclic radical having one or more rings incorporating one, two, or three heteroatoms within the ring (chosen from nitrogen, oxygen, or sulfur) which can optionally be substituted with hydroxy, cyano, lower alkyl, lower alkoxy, thioalkyl, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino and/or trifluoromethyl, unless
10 otherwise indicated. Examples of heteroaryl radicals include, but are not limited to, imidazolyl, oxazolyl, pyrazinyl, thiophenyl, quinolyl, benzofuryl, pyridyl, indolyl, pyrrolyl, pyranal, naphthyridinyl, and the like.

"Heterocyclyl" means the monovalent saturated carbocyclic radical, consisting of one or more rings, incorporating one, two, or three heteroatoms
15 (chosen from nitrogen, oxygen or sulfur), which can optionally be substituted with hydroxy, cyano, lower alkyl, lower alkoxy, thioalkyl, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino and/or trifluoromethyl, unless otherwise indicated. Examples of heterocyclic radicals include, but are not limited
20 to, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranal, thiomorpholinyl, and the like.

"Halogen" means the radical fluoro, bromo, chloro and/or iodo.

"Protective group" has the meaning conventionally associated with it in synthetic organic chemistry, *i.e.*, a group which selectively blocks one reactive site
25 in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotective reactive site. Certain processes of this invention rely upon the protective groups intended to protect the nitrogen atom against undesirable reactions during synthetic procedures and includes, but is not limited to, acetyl, benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), p-methoxy-
30 benzyloxy-carbonyl, N-*tert*-butoxycarbonyl (BOC), trifluoromethylcarbonyl, p-nitrobenzyloxy-carbonyl, and the like. It is preferred to use BOC or CBZ as the amino-protecting group because of the relative ease of removal, for example by

mild acids in the case of BOC, *e.g.*, trifluoroacetic acid or hydrochloric acid in ethyl acetate; or by catalytic hydrogenation in the case of CBZ.

5 "Deprotection" or "deprotecting" means the process by which a protective group is removed after the selective reaction is completed. Certain protective groups may be preferred over others due to their convenience or relative ease of removal.

10 "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present and that the description includes both single and double bonds.

15 "Inert organic solvent" or "inert solvent" means a solvent inert under the conditions of the reaction being described in conjunction therewith, including for example, benzene, toluene, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, chloroform (CHCl_3), methylene chloride or dichloromethane (CH_2Cl_2), dichloroethane, diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *tert*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

20 "Isomerism" means compounds that have identical molecular formulae but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are
25 non-superimposable mirror images are termed "enantiomers", or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a "chiral center".

30 "Chiral isomer" means a compound with one chiral center. It has two enantiomeric forms of opposite chirality and may exist either as an individual enantiomer or as a mixture of enantiomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric

pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn et al. *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn et al. *Angew. Chem.* 1966, 78, 413; Cahn and Ingold *J. Chem. Soc.* (London) 1951, 612; Cahn et al. *Experientia* 1956, 12, 81; Cahn, J. *Chem. Educ.* 1964, 41, 116).

"Geometric Isomers" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

"Atropic isomers" means the isomers owing their existence to restricted rotation caused by hindrance of rotation of large groups about a central bond.

A "pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition that is generally compatible with the other ingredients of the composition, not deleterious to the recipient, and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts, for example, include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic

acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like;

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methyl-glucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like;

(3) solvent addition forms or crystal forms of the same acid addition salt which are able to be formed. Such solvent addition forms or crystal forms, for example, include:

polymorphs, which are crystal structures in which a compound can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate.

solvates which are generally a crystal form that contains either stoichiometric or non-stoichiometric amounts of a solvent. Often, during the process of crystallization some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. For example, when

the solvent is water, hydrates may be formed; when the solvent is alcohol, alcoholates may be formed, etc.

amorphous solids which are noncrystalline materials with no long range order and generally do not give a distinctive powder X-ray diffraction pattern.

(4) internal salts formed when one or several nitrogen atoms of aliphatic or aromatic amines are oxidated to the N-oxide form such as N-oxides, in particular those N-oxides formed upon the oxidation of tertiary cyclic amines to give a chemically stable tertiary cyclic amine N-oxides, *e.g.*, the piperidine N-oxide; or

(5) quaternary salts formed when a negatively charged acid radical (the anion) joins a molecular structure which includes a central organic nitrogen atom joined to four organic groups (the cation).

The compounds of Formula I, their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included whenever a compound of Formula I or a salt thereof is referred to herein. Such hydrates are formed by the combination of one or more molecules of water with one of the compounds, in which the water retains its molecular state as H₂O, such combination being able to form one or more than one hydrate.

"Subject" means mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalia class: humans, non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs, and the like. Examples of non-mammals include, but are not limited to birds, and the like. The term does not denote a particular age or sex.

"Treating" or "treatment" of a disorder includes:

(1) preventing the disorder, *i.e.*, causing the clinical symptoms of the disorder not to develop in a subject that may be exposed to or predisposed to the disorder but does not yet experience or display symptoms of the disease,

5 (2) inhibiting the disorder, *i.e.*, arresting the development of the disorder or its clinical symptoms, or

(3) relieving the disorder, *i.e.*, causing temporary or permanent regression of the disorder or its clinical symptoms.

"Pharmacological effect" encompasses effects produced in the subject that achieve the intended purpose of a therapy. In one preferred embodiment, a
10 pharmacological effect means that pain symptoms of the subject being treated are prevented, alleviated, or reduced. For example, a pharmacological effect would be one that results in the reduction of pain in a treated subject. In another preferred embodiment, a pharmacological effect means that disorders or symptoms of the urinary tract of the subject being treated are prevented, alleviated, or reduced. For
15 example, a pharmacological effect would be one that results in the prevention or reduction of incontinence or pelvic hypersensitivity in a treated subject.

"Disease state" means any disease, condition, symptom, or indication.

"Disorders of the urinary tract" or "uropathy" used interchangeably with "symptoms of the urinary tract" means the pathologic changes in the urinary tract.
20 Examples of urinary tract disorders include, but are not limited to, incontinence, benign prostatic hypertrophy (BPH), prostatitis, detrusor hyperreflexia, outlet obstruction, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urge incontinence, urethritis, prostatodynia, cystitis, idiopathic bladder hypersensitivity, and the like. The particularly preferred
25 disorder of the urinary tract includes overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

"Overactive bladder" or "detrusor hyperactivity" includes, but is not limited to, the changes symptomatically manifested as urgency, frequency, reduced bladder capacity, incontinence episodes, and the like; the changes urodynamically
30 manifested as changes in bladder capacity, micturition threshold, unstable bladder contractions, sphincteric spasticity, and the like; and the symptoms usually

manifested in detrusor hyperreflexia (neurogenic bladder), in conditions such as outlet obstruction, outlet insufficiency, pelvic hypersensitivity, or in idiopathic conditions such as detrusor instability, and the like.

5 "Outlet obstruction" includes, but is not limited to, benign prostatic hypertrophy (BPH), urethral stricture disease, tumors and the like. It is usually symptomatically manifested as obstructive (low flow rates, difficulty in initiating urination, and the like), and irritative (urgency, suprapubic pain, and the like).

10 "Outlet insufficiency" includes, but is not limited to, urethral hypermobility, intrinsic sphincteric deficiency, or mixed incontinence. It is usually symptomatically manifested as stress incontinence.

"Pelvic Hypersensitivity" includes but is not limited to pelvic pain, interstitial (cell) cystitis, prostatic pain, vulvodynia, urethritis, orchialgia, and the like. It is symptomatically manifested as pain, inflammation or discomfort referred to the pelvic region, and usually includes symptoms of overactive bladder.

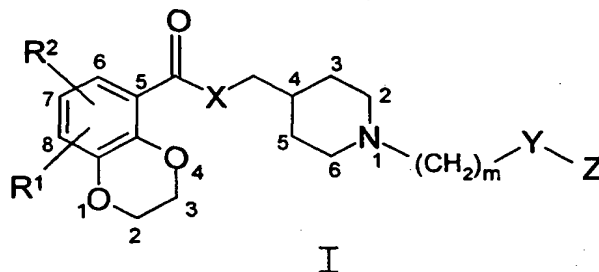
15 "Disorders of the Central Nervous System (CNS)" or "CNS disorder" means neurological and/or psychiatric changes in the CNS, *e.g.*, brain and spinal cord, which manifest in a variety of symptoms. Examples of CNS disorders, for example, include migraine headache, anxiety, depression, cerebrovascular deficiency, psychoses including paranoia, schizophrenia, attention deficiency, and
20 autism; obsessive/compulsive disorders including anorexia and bulimia; convulsive disorders including epilepsy and withdrawal from addictive substances; cognitive diseases including Parkinson's disease and dementia; and thermoregulation disorder.

25 "Disorders of the gastrointestinal system" or "GI disorders" means physiological changes in the alimentary tract. Examples of GI disorders, for example, include dyspepsia, gastric stasis, peptic ulcer, reflux esophagitis, gastritis, pseudo-obstruction syndrome, diverticulitis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, flatulence, diarrhea, and peristaltic disorders including disturbed colonic motility.

30 "Disorders of the cardiovascular system" or "CV disorders" means a physiological or pathological alteration in the cardiovascular system, in particular, improper cardiac chronotropy or arrhythmia. Examples of CV disorders, for

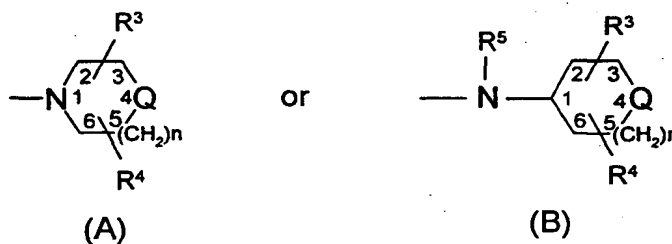
example include bradyarrhythmia, tachyarrhythmia, supraventricular arrhythmia, atrial fibrillation, atrial flutter, or atrial tachycardia.

The naming and numbering of the compounds of this invention is illustrated below:



5

The side chains of the Z substituent are numbered as shown below:



In general, the nomenclature used in this application is generally based on AutoNom, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. However, because a strict adherence to these recommendations would result in the names changing substantially when only a single substituent is changed, compounds have been named in a manner that maintains consistency of nomenclature for the basic molecule.

For example, a compound of Formula I wherein X is -NH, Y is -SO₂, m is 3, and Z is represented by formula (A) wherein Q is -NR⁶, n is 1, and R¹, R², R³ and R⁴ are each independently hydrogen, and R⁶ is methyl, is named 2,3-dihydrobenzo-[1,4]-dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl]piperidin-4-ylmethyl} amide.

15

For example, a compound of Formula I wherein X is $-\text{CH}_2$, Y is $-\text{SO}_2$, m is 3, and Z is represented by formula (A) wherein Q is O, n is 1, and R^1 , R^2 , R^3 and R^4 are each independently hydrogen, is named 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-3-{1-3-(morpholine-4-sulfonyl)propyl]piperidin-4-yl} propan-1-one.

5 Among the compounds of the present invention set forth in the Summary of the Invention, certain compounds of Formula I are preferred:

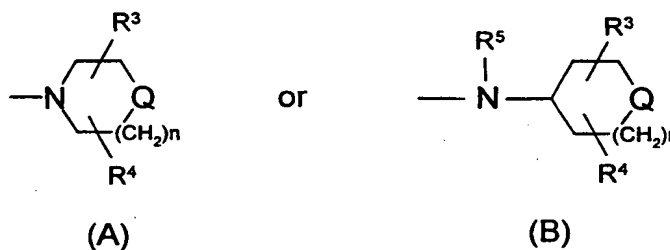
R^1 and R^2 are each independently in each occurrence hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, halogen, amino or hydroxy, more preferably hydrogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$, most preferably hydrogen;

10 X is $-\text{NH}$ or $-\text{CH}_2$, more preferably $-\text{NH}$;

m is 2, 3, or 4, more preferably 3;

Y is $-\text{SO}_2$;

Z is represented by formula (A) or (B), more preferably formula (A):



15 wherein:

R^3 , R^4 , and R^5 are each independently in each occurrence hydrogen or $(\text{C}_1\text{-C}_6)\text{alkyl}$, more preferably hydrogen;

Q is O, S, $-\text{NR}^6$ or $-\text{CR}^7\text{R}^8$, more preferably O, $-\text{NR}^6$, or $-\text{CR}^7\text{R}^8$, most preferably $-\text{NR}^6$;

20 n is 1 or 2; more preferably 1

wherein:

- R^6 is hydrogen, (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, heterocyclyl, heteroaryl, $-COR^9$, $-SO_2R^9$, $-CONR^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, or aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl, more preferably (C_1-C_6) alkyl, (C_3-C_8) cycloalkyl, $-SO_2R^9$, or aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl, most preferably (C_1-C_6) alkyl;
- R^7 is hydrogen or (C_1-C_6) alkyl, more preferably hydrogen;
- R^8 is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, aryloxy, $-(CH_2)_pCONR^{10}R^{11}$, $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^7COR^9$, or $-(CH_2)_pNR^7SO_2R^9$; more preferably (C_1-C_6) alkyl or (C_1-C_6) alkoxy, most preferably (C_1-C_6) alkyl; or
- R^7 and R^8 taken together with the common ring carbon to which they are attached form a monocyclic saturated 5- or 6-membered ring optionally independently containing 0 or 1 heteroatom of nitrogen, oxygen, or sulfur, more preferably taken together with the common ring carbon to which they are attached form a monocyclic saturated 5-membered ring optionally independently containing 0 heteroatom;

wherein:

p is 0, 1, 2, 3 or 4; more preferably 0 or 1, most preferably 0;

R^9 is (C_1-C_6) alkyl, heteroaryl, heterocyclyl, or aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl, more preferably (C_1-C_6) alkyl or aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl, most preferably aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl; and

R^{10} and R^{11} are each independently hydrogen or (C_1-C_6) alkyl, more preferably hydrogen.

Among the compounds of the present invention set forth in the Summary of the Invention, one preferred group of compounds of Formula I, designated "Group A", are those compounds wherein:

R^1 and R^2 are each independently hydrogen;

m is 3;

X is -NH; and

Z is formula (A), n is 1, and R³ and R⁴ are each independently hydrogen.

A first preferred subgroup among the Group A compounds are those compounds wherein:

5 Q is -NR⁶ wherein:

R⁶ is hydrogen, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, more preferably hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or cyclopentyl; most preferably methyl; or

10 R⁶ is aryl optionally mono- or di-substituted with halogen or (C₁-C₆)alkyl, or -SO₂R⁹; more preferably R⁶ and R⁹ are each independently phenyl, 4-fluorophenyl or 4-chlorophenyl.

A second preferred subgroup among the Group A compounds are those compounds wherein:

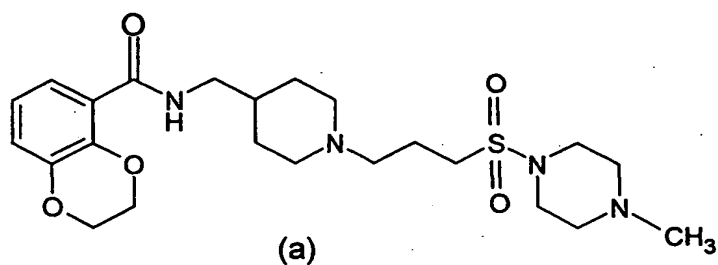
Q is -CR⁷R⁸ wherein:

15 R⁷ and R⁸ are each independently hydrogen or (C₁-C₆)alkyl, more preferably hydrogen, methyl, ethyl, or propyl; or

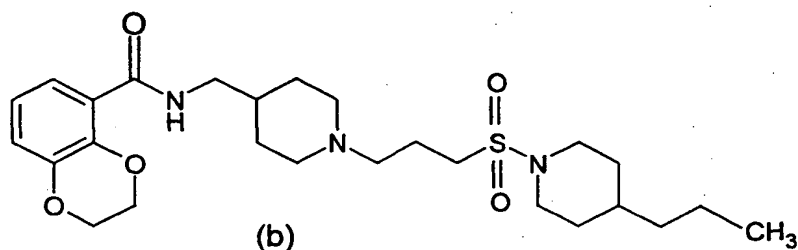
20 R⁷ and R⁸ taken together with the common ring carbon to which they are attached form a monocyclic saturated 5- or 6-membered ring optionally containing 0, or 1 heteroatom of nitrogen, oxygen, or sulfur; more preferably R⁷ and R⁸ taken together with the common ring carbon to which they are attached form a monocyclic saturated 5-membered ring containing 0 hetero-atoms.

25 Another preferred group of compounds of Formula I, designated "Group B", are those compounds wherein R¹ and R² are each independently hydrogen; Y is -SO₂, and m is 3; X is -CH₂; Z is formula (A), n is 1, and R³ and R⁴ are each independently hydrogen; and Q is O.

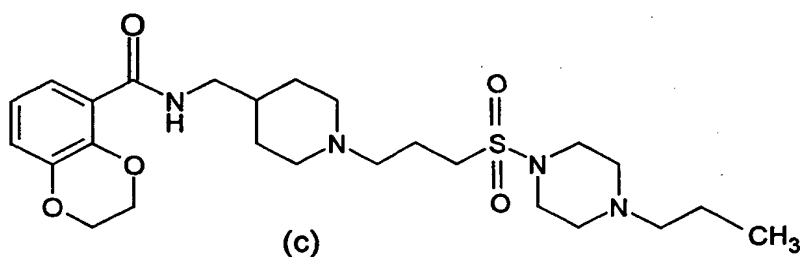
Exemplary particularly preferred compounds include:



2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

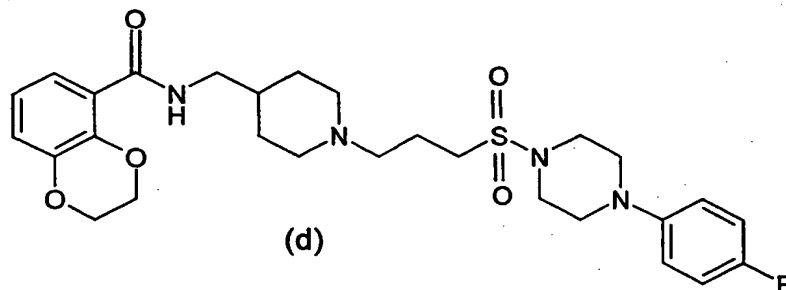


5 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-propylpiperidine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

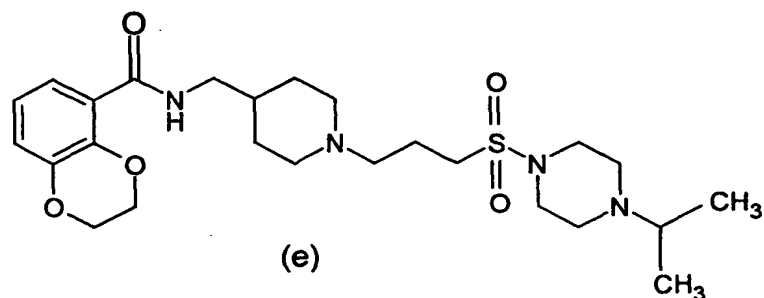


2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-propylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

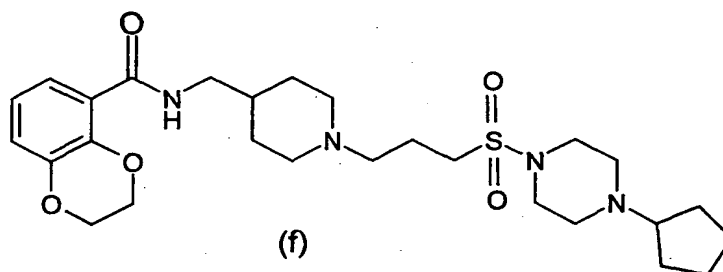
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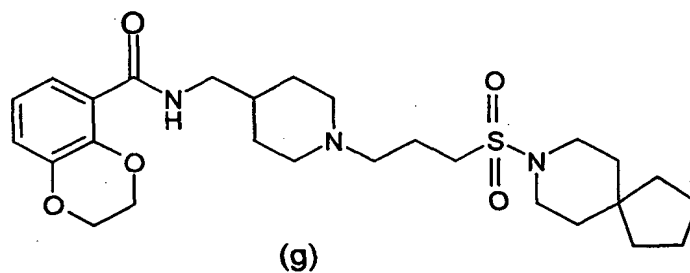
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(4-fluorophenyl)piperazine-1-sulfonyl]-propyl}piperidin-4-ylmethyl) amide;



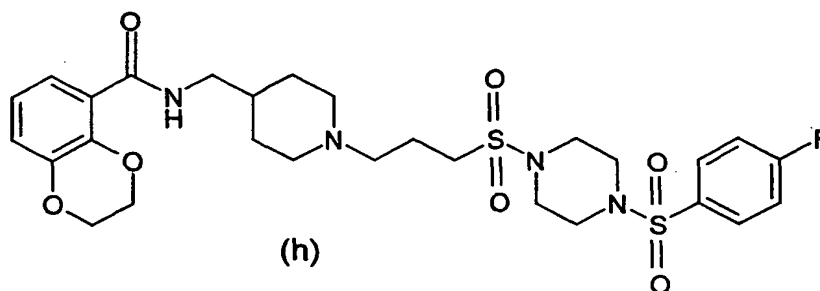
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-isopropylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;



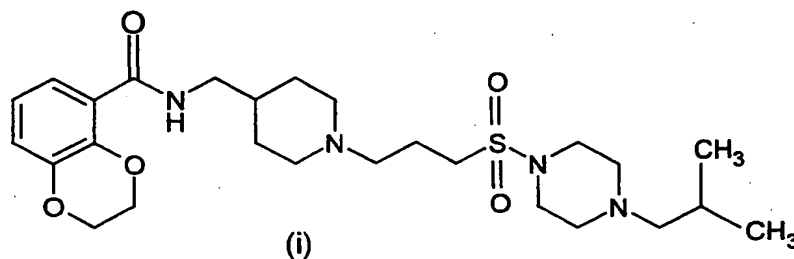
5 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-cyclopentylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;



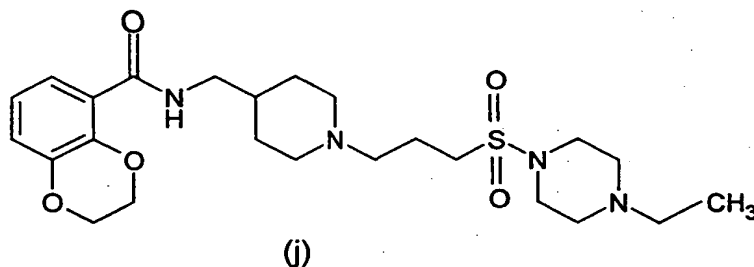
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(8-azaspiro[4.5]decane-8-sulfonyl)propyl] piperidin-4-ylmethyl} amide;



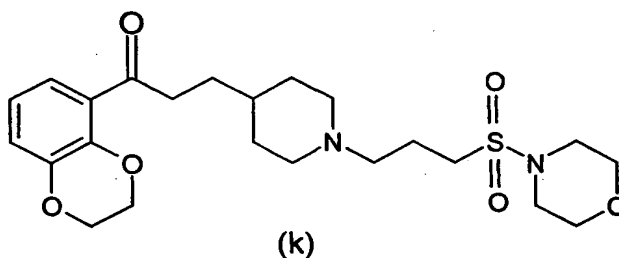
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(4-fluorobenzenesulfonyl)piperazine-1-sulfonyl]propyl}piperidin-4-ylmethyl) amide;



5 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-isobutylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;



2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-ethylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide; and

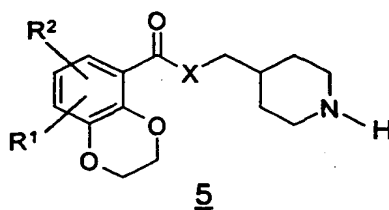


10 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl) 3-{1-[3-(morpholine-4-sulfonyl)propyl]piperidin-4-yl} propan-1-one.

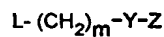
The novel compounds of formula I can be prepared by methods known in the art, for example by processes described below, which comprises

a) reacting a compound of formula

- 22 -



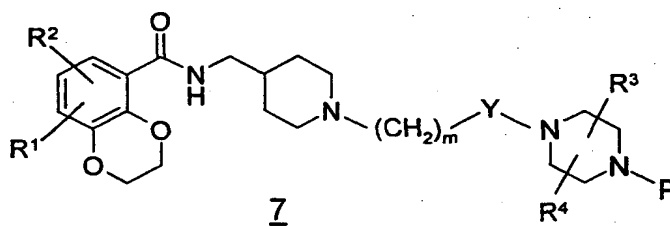
with a compound of formula



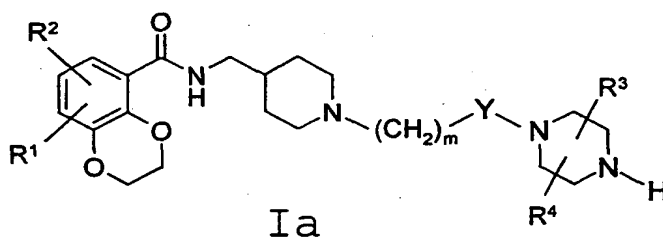
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- 5 to a compound of formula I,
wherein the substituents are described above, or

- b) deprotecting a compound of formula



to a compound of formula

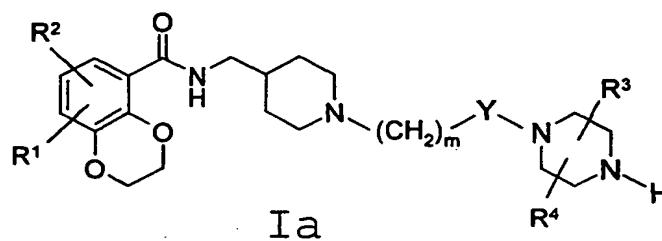


10

wherein the substituents are described above and P is a suitable protecting group,

or

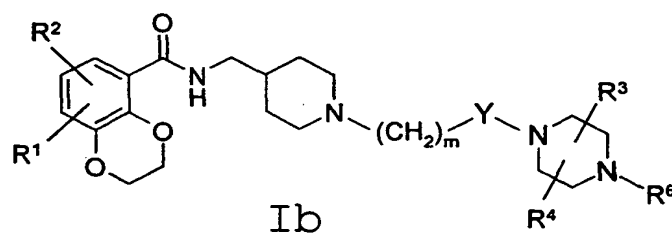
- c) alkylating a compound of formula



with an alkylating agent of formula



to a compound of formula

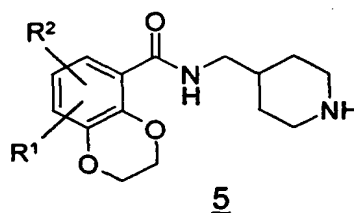


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wherein the substituents are described above and R^6 is other than hydrogen and L is a leaving group,

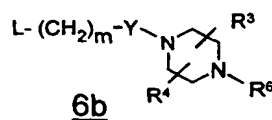
or

d) reacting a compound of formula

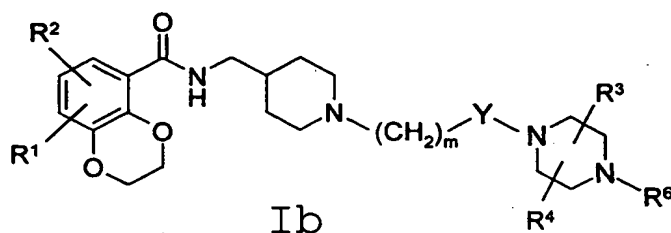


10

with a compound of formula



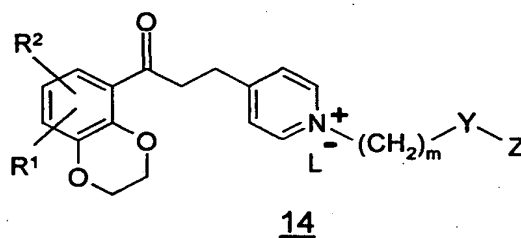
to a compound of formula



wherein the substituents are described above,

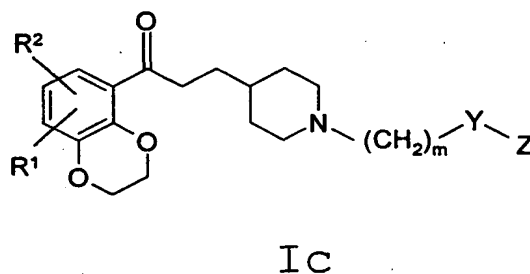
or

e) reducing a compound of formula



5

to a compound of formula



wherein the substituents are given above,

f) modifying one or more substituents within the definitions given above, and,

10 if desired, converting the compound obtained into a individual isomer or into a pharmaceutically acceptable salt or hydrate thereof.

In detail, compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

15 The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. or are prepared by methods known to those skilled in the art following procedures set

forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*, Wiley & Sons: New York, 1991, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and *Organic Reactions*, Wiley & Sons: New York, 1991, Volumes 1-40. These schemes are
5 merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

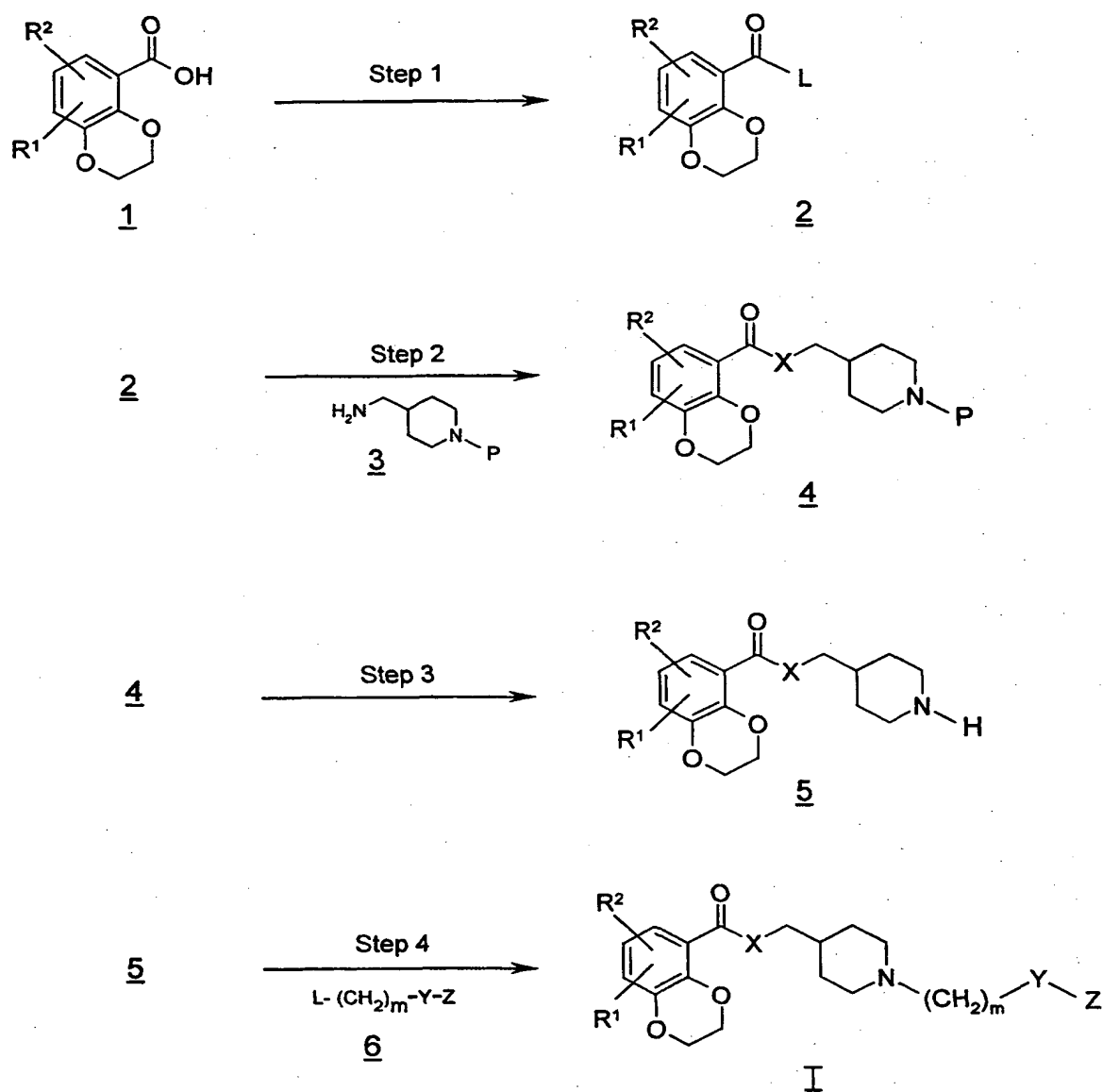
The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to
10 filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78°C to about 150°C ,
15 more preferably from about 0°C to about 125°C , and conveniently at about room (or ambient) temperature, e.g., about 20°C .

Schemes A, B, C, and D describe alternative methods to generate the compounds of Formula I.

Scheme A

Scheme A, in general, describes a method of preparing compounds of Formula I wherein X, Y and Z are as defined in the Summary of the Invention.



5

In general, the starting compounds of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid **1**, an activated carboxylic acid derivative **2**, and a protected (aminomethyl)piperidine **3** wherein P is a suitable protecting group such as benzyl,

tert-butoxycarbonyl (BOC) or carbobenzyloxy (CBZ), preferably BOC, are commercially available or known to or can readily be synthesized by those of ordinary skill in the art. For example, compound 1 can be prepared by the method described in Fuson *et al.*, *J. Org. Chem.* 1948, 13, 494; compound 3 wherein P is
5 BOC, can be prepared by the method described in Prugh *et al.*, *Synthetic Commun.* 1992, 22, 2357.

In step 1, an activated carboxylic acid derivative 2 wherein L is a leaving group such as chloro, is prepared by treating the compound 1 with a suitable chlorinating agent, *e.g.*, thionyl chloride or oxalyl chloride, under conditions well
10 known to one skilled in the art. Suitable solvents for the reaction include aprotic organic solvents such as dichloromethane, chloroform, dichloromethane, 1,2-dichloroethane or tetrahydrofuran, and the like.

In step 2, a protected (piperidin-4-ylmethyl)amide 4 wherein P is a suitable protecting group, preferably BOC, is prepared by reacting compound 2 with a
15 protected (aminomethyl)piperidine 3 under acylating conditions. The reaction proceeds in the presence of base such as triethylamine in a suitable inert organic solvent, for example dichloromethane, 1,2-dichloroethane, chloroform, tetrahydrofuran, and the like.

In step 3, a deprotected (piperidin-4-ylmethyl)amide 5 is prepared by
20 removing the protecting group from compound 4 by methods known to one of ordinary skill in the art. For example, when the protecting group is BOC, the deprotecting reaction proceeds by treatment with a strong organic acid such as trifluoroacetic acid in an inert organic solvent such as halogenated hydrocarbons including dichloromethane or 1,2-dichloroethane. For example, the deprotecting
25 reaction may also proceed by warming compound 4 in an 10% ethanolic hydrochloric acid solution.

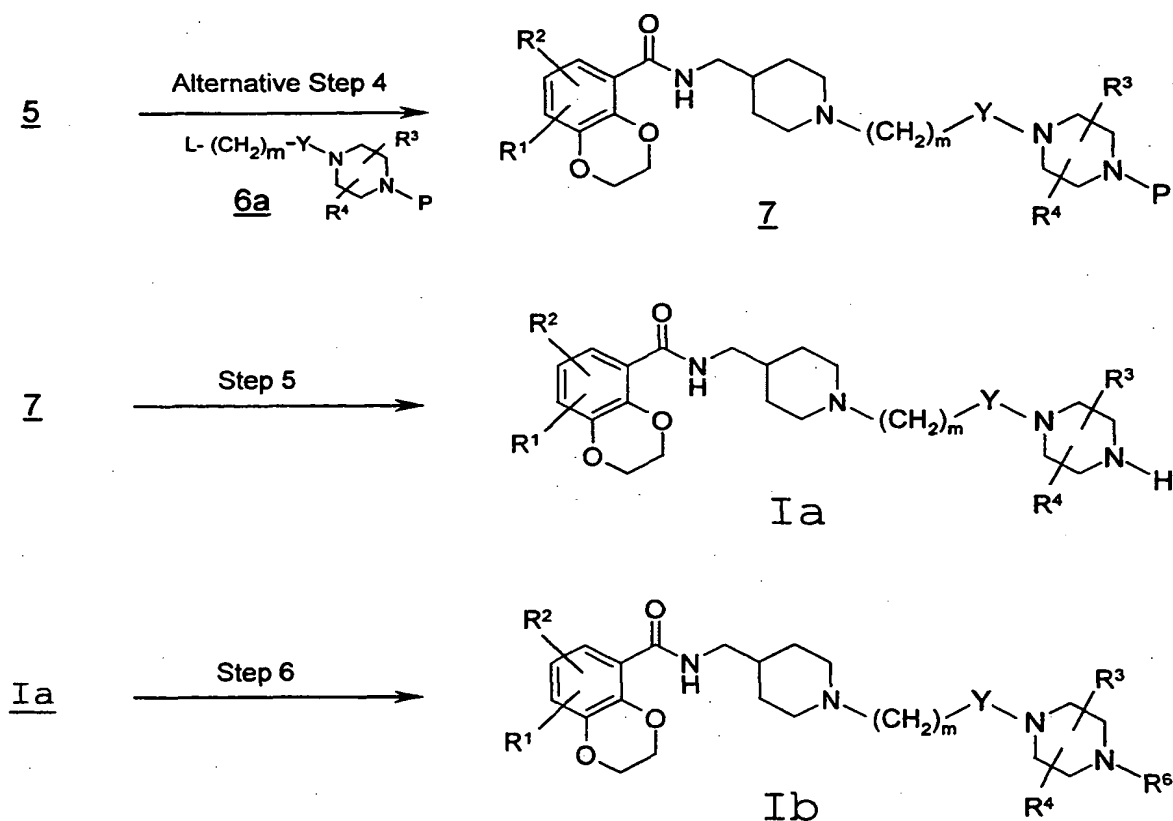
In step 4, a compound of Formula I is prepared by reacting compound 5 with an alkylating agent 6 wherein L is a leaving group, particularly halogen, under
30 alkylating conditions. The alkylating reaction proceeds in the presence of a base such as triethylamine and a catalyst such as sodium iodide. Suitable solvents for the reaction include aprotic organic solvents such as tetrahydrofuran,

N,N-dimethylformamide, acetonitrile, dimethyl sulfoxide, 1-methyl-2-pyrrolidinone, and the like.

Exemplary preparations of the following compounds utilizing the reaction conditions described in Scheme A are given. A compound of formula 4 is
5 described in Preparation 2, a compound of formula 5 is described in detail in Preparation 3A, a compound of formula 6 is described in Preparation 4, and a compound of Formula I is described in Example 1.

Scheme B

Scheme B describes an alternative method of preparing compounds of Formula I, in particular wherein X is -NH, Y is as described in the Summary of the Invention, and Z is represented by formula (A) wherein Q is -NR⁶ and R⁶ is as described in the Summary of the Invention.



Alternatively, a compound of Formula Ia or Ib can be prepared by utilizing the reaction conditions previously described in Scheme A, but substituting step 4 in Scheme A with alternative step 4 in Scheme B, and proceeding as in Scheme B above.

In alternative step 4, a protected piperazine compound 7 wherein P is a suitable protecting group, is prepared by reacting compound 5 with a protected alkylating agent 6a wherein L is a leaving group, particularly halogen, under alkylating conditions. The alkylating reaction proceeds in the same manner as described in Scheme A, step 4.

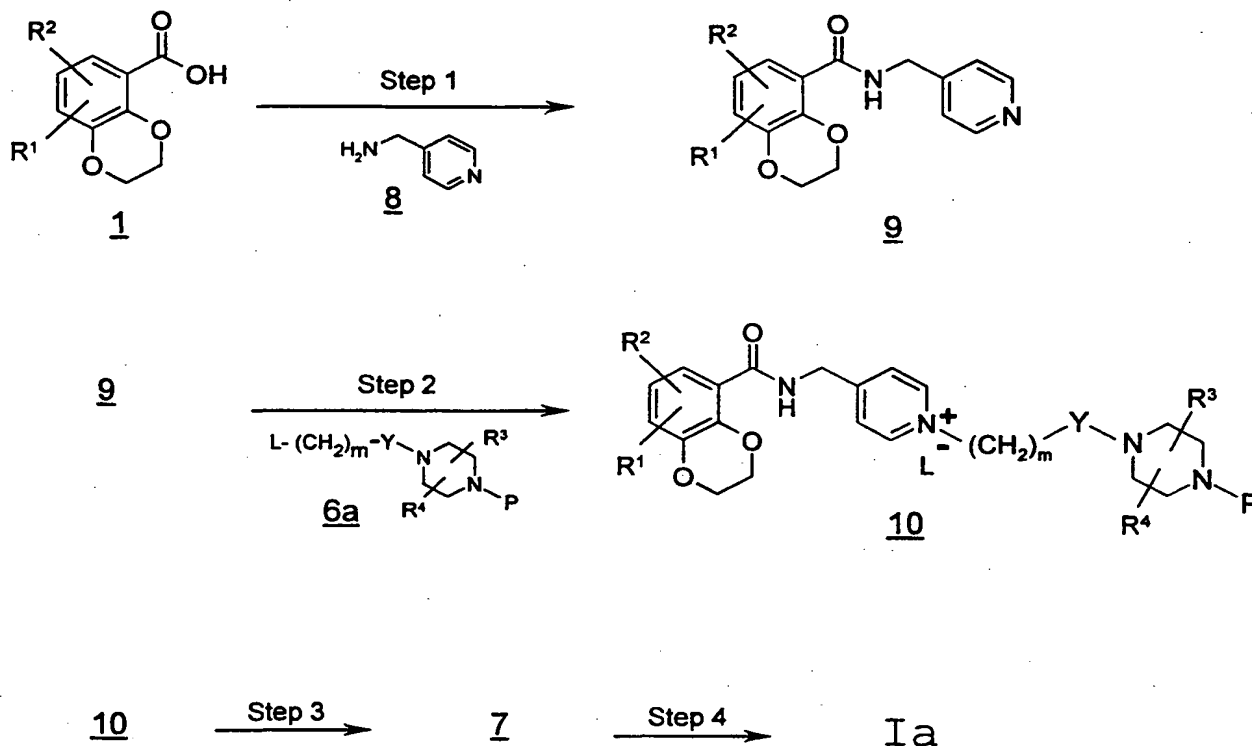
In step 5, a compound of Formula Ia is prepared by removing the protecting group from compound 7 by methods known to one of ordinary skill in the art. For example, when the protecting group is BOC, the deprotecting reaction proceeds in the same manner as described in Scheme A, step 3.

- 5 Optionally, in step 6, a compound of Formula Ib can be prepared by treating a compound of Formula Ia with an alkylating agent R^6L wherein R^6 is other than hydrogen and L is a leaving group such as halogen, under alkylating conditions, as described in Scheme A, step 4.

- 10 Exemplary preparations of the following compounds utilizing the reaction conditions described in Scheme B are given. Exemplary preparations of a compound of formula 6a is described in detail in Preparation 5, a compound of Formula Ia is described in detail in Example 2, and a compound of Formula Ib is described in Examples 4 and 5.

Scheme C

Scheme C describes an alternative method of preparing compounds of Formula I, in particular wherein X is -NH, Y is as described in the Summary of the Invention, and Z is represented by formula (A), and particularly wherein Q is -NR⁶ and R⁶ is hydrogen.



The starting compounds of formula 1 and an (aminomethyl)pyridine 8 are commercially available, for example from Aldrich Chemical Company, or known to or can readily be synthesized by those of ordinary skill in the art.

In step 1, a (pyridin-4-ylmethyl)amide 9 is prepared by acylating the (pyridin-4-ylmethyl)amine 8 with a carboxylic acid 1 in the presence of a coupling agent such as N,N'-carbonyldiimidazole (CDI), dicyclohexyl-carbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI). Suitable solvents for the reaction include aprotic organic solvents such as tetrahydrofuran, N,N-dimethylformamide, and the like.

In step 2, a pyridinium salt 10 is prepared by reacting compound 9 with a protected alkylating agent 6a wherein L is a leaving group, particularly halogen, under alkylating conditions previously described in Scheme A, step 4.

5 In step 3, the piperidinyll compound 7 is prepared by the reduction of compound 10. Suitable pyridinyl reducing conditions include catalytic hydrogenation, for example Raney nickel, or platinum or palladium catalyst, (e.g., PtO₂ or Pd/C) in a protic organic solvent such as methanol or ethanol.

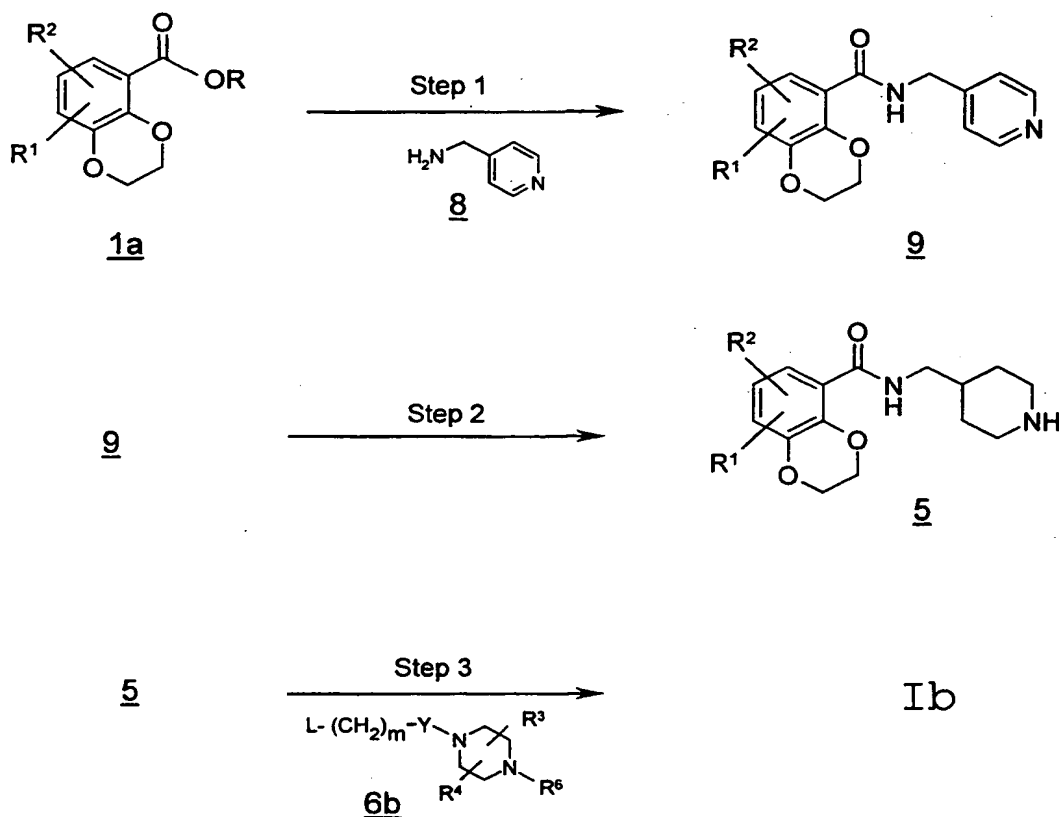
In step 4, a compound of Formula Ia is prepared from compound 8 utilizing the methods described in Scheme B.

10 Exemplary preparations of the following compounds utilizing the reaction conditions described in Scheme C are given. Exemplary preparations of a compound of formula 6a is described in detail in Preparation 5, a compound of formula 9 is described in detail in Preparation 7A, and a compound of Formula Ia is described in detail in Example 3.

15

Scheme D

Scheme D describes an alternative method of preparing compounds of Formula I, in particular wherein X is -NH, Y is as described in the Summary of the Invention, and Z is represented by formula (A), and particularly wherein Q is -NR⁶ and R⁶ is other than hydrogen.



The starting compounds of a carboxylic acid ester **1a** and an (aminomethyl)pyridine **8** are commercially available, or known to or can readily be synthesized by those of ordinary skill in the art. For example, the carboxylic acid ester **1a** can be prepared by methods known in the art such as by the esterification of the corresponding carboxylic acid, or by the esterification of a 2,3-dihydroxybenzoic acid, and subsequent cyclization of the 2,3-dihydroxy-benzoic acid ester in a suitable solvent such as 1,2-dichloroethane under phase-transfer reaction conditions.

In step 1, a (pyridin-4-ylmethyl)amide 9 is prepared by acylating a (pyridin-4-ylmethyl)amine 8 with a carboxylic acid ester 1a in the presence a strong base such as sodium methoxide in a suitable protic organic solvent such as methanol.

5 In step 2, a (piperidin-4-ylmethyl)amide 5 is prepared by reducing the pyridinyl group of compound 9 to a piperidinyl group. Suitable pyridinyl reducing conditions include catalytic hydrogenation, for example Raney nickel, or platinum or palladium catalyst, (e.g., PtO₂ or Pd/C) in a protic organic solvent such as methanol or ethanol.

10 Alternatively, a (piperidin-4-ylmethyl)amide 5 can be prepared by treating the carboxylic acid ester 1a with a lithiated (aminomethyl)piperidine (prepared by treating the (aminomethyl)piperidine with an organometallic reagent such as n-butyllithium in an aprotic solvent such as tetrahydrofuran under conditions well known in the art). The reaction proceeds at a temperature of about 25° to 100 °C.

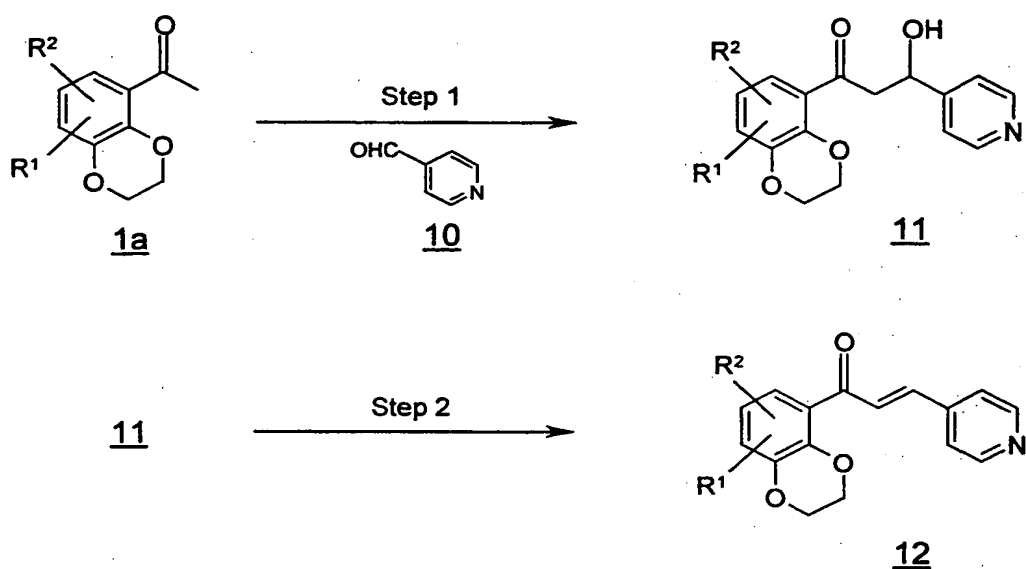
15 Alternatively, a (piperidin-4-ylmethyl)amide 5 can be prepared by treating the carboxylic acid ester 1a with an (aminomethyl)piperidine in the presence of a strong base such as sodium methoxide in a protic organic solvent such as methanol.

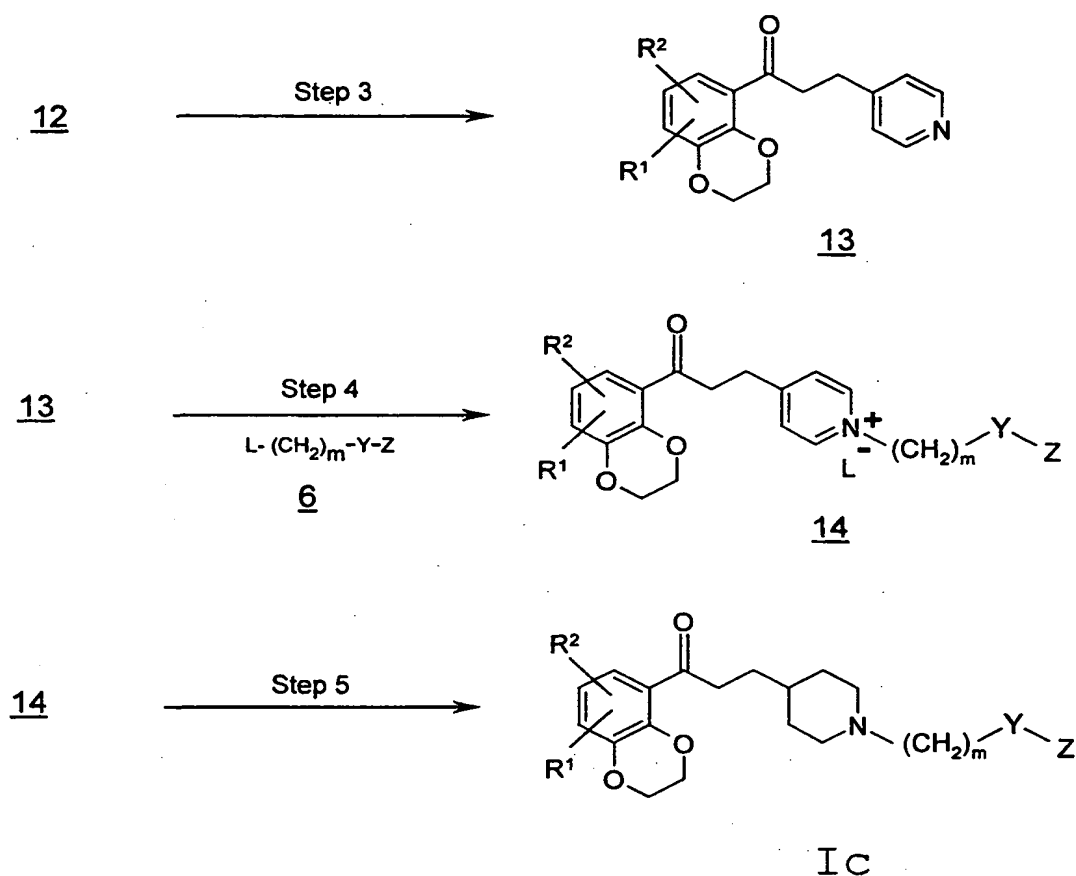
20 In step 3, a compound of Formula Ib is prepared by treating compound 5 with an alkylating agent 6a wherein L is a leaving group, particularly halogen, under alkylating conditions. The reaction proceeds under phase transfer conditions in the presence of a base such as potassium carbonate, sodium carbonate, sodium hydroxide, or trisodium phosphate, a phase transfer catalyst such as *tetra*-n-butylammonium bromide, and a reaction enhancer such as potassium bromide. Preferable solvent systems for the reaction include
25 toluene/water and the like.

30 Exemplary preparations of the following compounds utilizing the reaction conditions described in Scheme D are given. Exemplary preparations of a compound of formula 1a is described in detail in Preparation 1, a compound of formula 5 is described in detail in Preparation 3B, 3C, and 3D, a compound of formula 6b is described in detail in Preparation 6, a compound of formula 9 is described in detail in Preparation 7B, and a compound of Formula Ib is described in detail in Example 6.

Scheme E

Scheme E describes an alternative method of preparing compounds of Formula I, in particular wherein X is -CH₂, Y and Z are as described in the Summary of the Invention.





The starting compound of a (2,3-dihydrobenzo[1,4]dioxin-5-yl) ketone 1a can readily be synthesized from 2,3-dihydrobenzo[1,4]dioxine by methods known to one of ordinary skill in the art, for example, by methods similarly described
 5 U.S. Patent No. 5,763,458.

The starting compound of pyridine-4-carboxaldehyde 10 is commercially available, for example, from Aldrich Chemical Company, or known to or can readily be synthesized by those of ordinary skill in the art.

In step 1, a pyridinyl β -hydroxy ketone 11 is prepared by reacting compound
 10 1a with compound 10 under aldol condensation reaction conditions, preferably in the presence of a base such as lithium diisopropylamide. The reaction proceeds at a reduced temperature of about -20° to 0°C in a suitable aprotic organic solvent such as tetrahydrofuran, diethyl ether, and the like.

In step 2, a pyridinyl enone 12 is prepared by dehydrating the alcohol group of compound 14 to an alkene group under conditions well known to one skilled in the art. The elimination reaction proceeds in the presence of an acid such as sulfuric acid, hydrochloric acid, or a Lewis acid.

5 In step 3, a pyridinyl ketone 13 is prepared by the hydrogenation of the alkene group of compound 12 to an alkyl group under conditions well known to one skilled in the art. Suitable hydrogenation conditions include catalytic hydrogenation using a platinum or palladium catalyst (e.g., PtO₂ or Pd/C) in a protic organic solvent such as methanol, ethanol, ethyl acetate, and the like.

10 In step 4, a pyridinium salt 14 is prepared by reacting compound 13 with an alkylating agent 6 wherein L is a leaving group, particularly halogen, under alkylating conditions previously described in Scheme A, step 4.

In step 5, a compound of Formula Ic is prepared by the reduction of pyridinyl group of compound 14 to a piperidinyl group. Suitable pyridinyl
15 reducing conditions include catalytic hydrogenation, for example Raney nickel or platinum or palladium catalyst (e.g., PtO₂ or Pd/C) in an alcoholic solvent such as methanol or ethanol.

Exemplary preparations of the following compounds utilizing the reaction conditions described in Scheme E are given. A compound of formula 11 is
20 described in Preparation 8, a compound of formula 12 is described in Preparation 9, a compound of formula 13 is described in Preparation 10, and a compound of Formula Ic is described in Example 7.

The compounds of Formula I are 5-HT₄ receptor antagonists and are useful for treating disorders which can be ameliorated by interaction with 5-HT₄
25 receptors. For example, the compounds of Formula I can block 5-HT₄ receptor mediated peristalsis and are useful in treating diseases involving hypermotility states, or can block 5-HT₄ receptor mediated enhancement of neurogenic contractions of detrusor smooth muscle and are useful in the treatment of diseases involving overactive bladder (or detrusor hyperactivity), or can block 5-HT₄
30 receptor mediated positive chronotropy and are useful as antiarrhythmic agents. Thus, the compounds of Formula I are useful for treating a variety of disorders

including urinary tract disorders, CNS disorders, gastrointestinal disorders, and cardiovascular disorders.

Particular urinary tract disorders include diseases, conditions, or symptoms which relate directly or indirectly to dysfunction of urinary bladder smooth muscle or its innervation causing disordered urinary storage or voiding control such as overactive bladder, outlet obstruction, outlet insufficiency, and pelvic hypersensitivity (see Ford, A.P.D.W. and Kava, *supra*). Overactive bladder disorders include, but are not limited to, changes symptomatically manifested as urgency, frequency, reduced bladder capacity, incontinence, detrusor hyperreflexia (neurogenic bladder) or detrusor instability. Additionally, overactive bladder disorders include, but are not limited to changes urodynamically manifested as altered bladder capacity and micturition threshold, unstable bladder contractions, or sphincteric spasticity. Outlet obstruction disorders include, but are not limited to, benign prostatic hyperplasia (BPH), urethral stricture disease, tumors, which are symptomatically manifested as, for example, obstructive (low flow rates, difficulty in initiating urination) or irritative symptoms (urgency, suprapubic pain). Outlet insufficiency disorders include, but are not limited to, urethral hypermobility or intrinsic sphincteric deficiency, and are symptomatically manifested as stress incontinence. Pelvic hypersensitivity disorders include, but are not limited to, changes symptomatically manifested as pelvic pain or discomfort, interstitial cell cystitis, prostatic dysuria, prostatitis, vulvodynia, urethritis, orchialgia, or symptoms related to overactive bladder disorders.

Particular CNS disorders include diseases, conditions, or symptoms which include a variety of neurologic and psychiatric disorders such as cognitive disorders, psychoses, and obsessive/compulsive and anxiety/depression behavior. Cognitive disorders include attentional or memory deficits, dementia states, cerebral vascular deficiency and Parkinson's disease. Psychoses which may be treatable with the compounds of this invention include paranoia, schizophrenia and autism. Obsessive/compulsive behavior includes eating disorders, for example bulimia. Anxiety/depressive states include anticipatory anxiety (*e.g.*, prior to surgery, dental work, *etc.*), depression, mania, seasonal affective disorder (SAD), and the convulsions and anxiety caused by withdrawal from addictive substances such as opiates, benzodiazepines, nicotine, alcohol, cocaine and other drugs of abuse.

Particular gastrointestinal disorders include diseases, conditions, or symptoms which relate directly or indirectly to motility of the stomach, esophagus, and of both the large and small intestines (see Hegde, S.S., *supra*). Specific disorders include, but are not limited to, dyspepsia, gastric stasis, peptic ulcer, reflux esophagitis, flatulence, bile reflux gastritis, pseudo-obstruction syndrome, irritable colon syndrome, diverticular disease, biliary dysmotility, gastroparesis, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), Crohn's disease, and retarded gastric emptying. Other uses include short-term prokinesis to facilitate diagnostic radiology and intestinal intubation, and for treating chronic and acute diarrhea, particularly diarrhea induced by cholera and carcinoid syndrome.

Particular cardiovascular disorders include diseases, conditions, or symptoms which relate directly or indirectly to cardiac arrhythmias (e.g., supraventricular arrhythmia, atrial fibrillation, atrial flutter, atrial tachycardia).

The 5-HT₄ receptor antagonist activity of the test compounds can be identified by an *in vitro* assay which utilizes isolated thoracic esophagus muscle in the rat. This assay is well-established as a model for identifying and characterizing compounds that interact with 5-HT₄ receptors (e.g., see Baxter, G.S. *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1991, 343, 439-446), and is described in more detail in Example 15.

The 5-HT₄ receptor antagonist properties of the test compounds can be identified by an *in vivo* assay by determining the inhibitory activity on 5-HT induced heart rate increases in anesthetized and vagotomized Yucatan micropigs (e.g., see Eglen *et al.*, *Br. J. Pharmacol.* 1993, 108, 376-382) and is described in more detail in Example 16.

The invention includes a pharmaceutical composition comprising a compound of the present invention or individual isomers, racemic or non-racemic mixture of isomers, or pharmaceutically acceptable salts or hydrates thereof, together with one or more pharmaceutically acceptable carriers, and optionally other therapeutic and/or prophylactic ingredients.

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration

for agents that serve similar utilities. Suitable dosage ranges are 1-500 mg daily, preferably 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compounds of this invention for a given disease.

In general, compounds of this invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may comprise of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical composition may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing one (1) milligram of active ingredient or, more broadly, 0.01 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions

and dosage forms may comprise the compounds of the invention or its pharmaceutically acceptable salt or a crystal form thereof as the active component. The pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably containing from one to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in

addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous
5 infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include
10 propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution
15 before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with
20 an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles
25 comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid
30 glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

5 The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an
10 appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

 The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal
15 administration. The compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane,
20 trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch,
25 starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of *e.g.*, gelatin or blister packs from which the powder may be administered by means of an inhaler.

30 When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient.

 The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate

quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described in Examples 8 to 14.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

PREPARATION 1

2,3-Dihydrobenzo[1,4]dioxin-5-carboxylic acid ethyl ester

The following is the preparation of a compound of formula 1a wherein R^1 and R^2 are each independently hydrogen, and R is ethyl.

A mixture of 2,3-dihydroxybenzoic acid (994 g), ethanol (3.8 L) and sulfuric acid (320 g) was refluxed for 44 hours. A portion of the solvent distilled out of the solution, and the solution was cooled and stirred overnight, and then further cooled in an ice/water bath. To the solution was added water (5.6 L). The solution was aged, and the crystals were filtered, washed with water, and dried to give ethyl 2,3-dihydroxybenzoate (1002 g, 85%); m.p. 66.0-67.2 °C.

A mixture of ethyl 2,3-dihydroxybenzoate (1000 g), *tetra-n*-butyl-ammonium bromide (880 g), potassium carbonate (1552 g), 1,2-dichloroethane (3216 g), and water (10 kg) was refluxed for 5 hours. The solution was cooled and extracted with toluene. The extract was washed with a solution of 1N hydrochloric

acid and sodium chloride. The solution was partially concentrated and filtered through silica gel (300 g). The filtrate was concentrated to give the title compound (1074 g, 94%); m.p. 48-51 °C.

PREPARATION 2

5 4-[[[(2,3-Dihydrobenzo[1,4]dioxin-5-carbonyl)amino]methyl]piperidine-1-carboxylic acid *tert*-butyl ester

The following is the preparation of a compound of formula 4 wherein R¹ and R² are each hydrogen, X is -NH, and P is BOC.

A suspension of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (prepared
10 by the method described in Fuson *et al.*, *J. Org. Chem.* 1948, 13, 494) (16.4 g, 100 mmol) in dichloromethane (100 mL) was treated with oxalyl chloride (10.8 mL, 125 mmol) and N,N-dimethylformamide (5 drops). The reaction mixture was stirred at room temperature for 4 hours and then concentrated *in vacuo*. The resulting crystalline acid chloride was dissolved in dichloromethane (250 mL),
15 cooled in an ice-bath. Triethylamine (21 mL, 150 mmol) was added followed by dropwise addition of a solution of 4-(aminomethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (prepared by the method described in Prugh *et al.*, *Synthetic Commun.* 1992, 22, 2357) (21.4 g, 100 mmol). The stirred mixture was allowed to warm to room temperature over 2 hours and was then washed with water, dilute
20 hydrochloric acid and brine, dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was recrystallized from ethyl acetate-cyclohexane to give the title compound as a white solid (27.8 g, 76%); m.p. 103-105 °C. Analysis for C₂₀H₂₈N₂O₅: Calcd. : C, 63.81; H, 7.50; N, 7.44. Found: C, 64.01; H, 7.50; N, 7.56.

PREPARATION 3

25 2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid (piperidin-4-ylmethyl) amide

The following is the preparation of a compound of formula 5 wherein R¹ and R² are each hydrogen, and X is -NH.

A. A solution of the 4-[[[(2,3-dihydrobenzo[1,4]dioxin-5-carbonyl)amino]methyl]piperidine-1-carboxylic acid *tert*-butyl ester (36.6 g, 100 mmol) in

dichloromethane (50 mL) was treated with trifluoroacetic acid (50 mL) and the resulting solution was stirred at room temperature for 1 hour. Copious amounts of gas were evolved. The mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and brine, and the aqueous layer was
5 basified by the addition of aqueous ammonium hydroxide. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined dichloromethane extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as an amorphous powder (27 g, 98%). A hydrochloride salt was prepared from ethanol-ether; m.p. 216-217 °C. Analysis for
10 $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_3 \cdot \text{HCl} \cdot 0.1 \text{H}_2\text{O}$: Calcd.: C, 57.27; H, 6.79; N, 8.90. Found: C, 56.95; H, 6.79; N, 9.24.

B. A mixture of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (pyridin-4-ylmethyl) amide (50 g), platinum oxide (1.26 g), isopropanol (300 mL), and concentrated hydrochloric acid (30.83 mL) was stirred at a temperature of 45 °C
15 under a hydrogen atmosphere for 10 hours. The mixture was filtered, and the filtrate was diluted with isopropanol (350 mL) and concentrated. The concentrate was diluted with isopropanol (400 mL) and concentrated. The remaining solution was cooled slowly to -10 °C, filtered, washed with cold isopropanol and hexanes, and dried to give the title compound (46 g, 80%); m.p. 201.9-202.5 °C.

C. To a cooled solution of 4-(aminomethyl)piperidine (1053 g) in tetrahydrofuran (7 L) was slowly added a solution of n-butyllithium in hexanes (1.6M, 3.97 kg) and a solution of 2,3-dihydrobenzo[1,4]-dioxine-5-carboxylic acid ethyl ester (1067 g) dissolved in tetrahydrofuran (1.5 L). The reaction mixture was stirred in a cold bath for an hour and then at 40 °C for about a day, diluted with
25 water (5 L), and concentrated. To the concentrate was slowly added concentrated hydrochloric acid (2.46 kg). The solution was washed with dichloromethane, and sodium hydroxide (50%, 1.53 kg) was added. The solution was extracted with dichloromethane, and the extract was washed with sodium hydroxide (1N, 2 L), dried (Na_2SO_4), filtered, and concentrated. The concentrate was diluted with
30 toluene (10 L), concentrated, and slowly cooled to form crystals. The crystals were filtered, washed with toluene and dried to give the title compound (507 g, 40%).

D. A mixture of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid ethyl ester (1.7 g), toluene (5 mL), 4-(aminomethyl)piperidine (0.94 g), and sodium methoxide in methanol (25%, 1.8 g) were stirred for 5 hours. The mixture was diluted with water (10 mL) and concentrated hydrochloric acid (1.7 mL). The mixture was washed with dichloromethane (10 mL), and 50% sodium hydroxide was added. The mixture was extracted with dichloromethane, and the extract was dried (MgSO₄), filtered and concentrated to give the title compound (1.6 g, 70%).

PREPARATION 4

1-(3-Chloropropane-1-sulfonyl)-4-(4-fluorophenyl)piperazine

The following is the preparation of a compound of formula 6 wherein L is chloro, m is 3, Y is -SO₂, and Z is (4-fluorophenyl)-piperazine.

To a 0 °C solution of 1-(4-fluorophenyl)piperazine (6.4 g, 35 mmol) in dichloromethane (50 mL) was added 3-chloropropanesulfonyl chloride (6.5 g, 37 mmol). The mixture was stirred for 2 hours with warming to room temperature and was then washed with saturated aqueous sodium bicarbonate. The dichloromethane solution was dried (Na₂SO₄) and evaporated *in vacuo*. Recrystallization of the crystalline residue from methanol gave the title compound as a white solid (9.2 g, 80%); m.p. 80-81 °C.

PREPARATION 5

4-(3-Chloropropane-1-sulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester

The following is the preparation of a compound of formula 6a wherein R³ and R⁴ are each hydrogen, L is chloro, m is 3, Y is -SO₂, and P is BOC.

To a 0 °C solution of piperazine-1-carboxylic acid *tert*-butyl ester (4.7 g, 25 mmol) and triethylamine (7 mL, 50 mmol) in dichloromethane (50 mL) was added 3-chloropropanesulfonyl chloride (4.4 g, 25 mmol). The mixture was stirred for 2 hours with warming to room temperature and was then washed sequentially with dilute aqueous hydrochloric acid and saturated aqueous sodium bicarbonate. The dichloromethane solution was dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a white solid (7.4 g, 91%); m.p. 112-114 °C.

PREPARATION 6

1-(3-Chloropropane-1-sulfonyl)-4-methylpiperazine

The following is the preparation of a compound of formula 6b wherein R^3 and R^4 are each hydrogen, L is chloro, m is 3, Y is $-SO_2$, and Z is 4-methylpiperazine.

To a cooled solution of N-methylpiperazine (8.49 g), toluene (43 mL), and sodium hydroxide (25%, 43 mL) was added a solution of 3-chloropropanesulfonyl chloride (15 g) in toluene (30 mL) over a period 30 minutes. The mixture was stirred for 1 hour in a cold bath and then for another hour at room temperature. The top organic layer was separated, washed with aqueous sodium chloride, dried ($MgSO_4$), filtered, and concentrated to give the title compound (17.9 g, 88%); m.p. 43.0-44.5 °C.

PREPARATION 7

2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid (pyridin-4-ylmethyl) amide

The following is the preparation of a compound of formula 9 wherein R^3 and R^4 are each independently hydrogen.

A. N,N'-Carbonyldiimidazole (1.62 g, 10 mmol) was added to a stirred solution of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1.64 g, 10 mmol) in tetrahydrofuran (25 mL) and the resulting solution was heated at 60 °C for 15 minutes. The solution was cooled to room temperature and 4-(aminomethyl)pyridine (1.08 g, 10 mmol) was added. The reaction mixture was heated at 60 °C for 2 hours, cooled, poured into water, and extracted 3 times with ethyl acetate. The combined ethyl acetate extract was dried (Na_2SO_4) and evaporated *in vacuo* to a crystalline residue which was triturated with water, filtered, and dried *in vacuo* to give 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (pyridin-4-ylmethyl)amide as a white solid (1.95 g, 72%); m.p. 120-121 °C.

B. To a mixture of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid ethyl ester (1087 g), methanol (500 mL) and toluene (44 g) at 35 °C was added 25% sodium methoxide in methanol (1193 mL). After 30 minutes, 4-(aminomethyl)pyridine (530 mL) was added, and the reaction mixture was warmed to a temperature of 50

°C, maintained at 50 °C for 7 hours, and cooled to room temperature overnight. The reaction was then warmed to

30 °C and water (4.35 L) was added slowly over 40 minutes. The mixture was again cooled and aged at 5 °C overnight and filtered. The crystals were washed
5 with water, and dried to give the title compound (1255 g, 89%); m.p. 123-124.5 °C.

PREPARATION 8

1-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-3-hydroxy-3-pyridin-4-ylpropan-1-one

The following is the preparation of a compound of formula 11 wherein R¹ and R² are each independently hydrogen.

10 To a -60 °C solution of diisopropylamine (3.22 mL, 23 mmol) in tetrahydrofuran (35 mL) was added n-butyllithium (1.6 M in hexane, 14.4 mL). To the resulting solution was added 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)ethanone (prepared by the method described in U.S. Patent No. 5,763,458) (3.56 g,
15 20 mmol) in tetrahydrofuran (3 mL). The mixture was stirred at -60 °C for 10 minutes followed by the addition of pyridine-4-carboxaldehyde (2.36 g, 22 mmol). After stirring for an additional 40 minutes, the reaction mixture was treated with aqueous ammonium chloride solution, diluted with cold water, basified, and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried, and the concentrated *in vacuo* to afford the
20 crude title compound as a syrup which solidified (4.4 g, 77%). The product was directly used in the next step.

PREPARATION 9

1-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-3-pyridin-4-ylpropenone

25 The following is the preparation of a compound of formula 12 wherein R¹ and R² are each independently hydrogen.

To a cold solution of concentrated sulfuric acid (10 mL) was added 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-3-hydroxy-3-pyridin-4-ylpropan-1-one (2.0 g). The reaction mixture was stirred at a temperature of about 10-20 °C for 30 minutes, then allowed to cool in an ice bath and stirred for an additional

15-30 minutes. The resultant solid was filtered, washed several times with water, and dried. The residue was suspended in cold water, basified with ammonium hydroxide, and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and solvent evaporated *in vacuo* to give the title compound as a syrup (3.9 g) which was directly used in the next step.

PREPARATION 10

1-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-3-pyridin-4-ylpropan-1-one

The following is the preparation of a compound of formula 13 wherein R^1 and R^2 are each independently hydrogen.

A solution of 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-3-pyridin-4-ylpropanone (3.9 g, 14.59 mmol) in ethyl acetate (70 mL) was hydrogenated over 10% palladium on carbon (0.4 g) at atmospheric pressure for 5 hours. The catalyst was removed by filtration through Celite® and the filtrate concentrated *in vacuo* to give the title compound as a yellow solid (2.75 g, 51% overall yield); ^1H NMR (CDCl_3) 8.48 (dd, 2H), 7.29 (dd, 1H), 7.17 (dd, 2H), 7.02 (dd, 1H), 6.87 (dd, 1H), 4.30 (m, 4H), 3.30 (t, 2H), 3.02 (t, 2H).

EXAMPLE 1

20 2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4(4-fluorophenyl)-piperazine-1-sulfonyl]-propyl}piperidin-4-ylmethyl) amide

The following is the preparation of a compound of Formula I wherein R^1 and R^2 are each independently hydrogen, X is -NH, m is 3, Y is -SO₂, and Z is (4-fluorophenyl)-piperazine.

25 A mixture of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (piperidin-4-ylmethyl) amide (426 mg, 1.54 mmol), 1-(3-chloropropane-1-sulfonyl)-4-(4-fluorophenyl)piperazine (495 mg, 1.54 mmol), sodium iodide (230 mg, 1.54 mmol), and triethylamine (200 mg, 2 mmol) in N,N-dimethylformamide (5 mL) was stirred at 85 °C for 12 hours. The cooled reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The

ethyl acetate layer was washed with water (three times) and brine, and the organic layer dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by silica gel chromatography (5% methanol-dichloromethane) to give the title compound (350 mg, 40%). The dihydrochloride salt of the title compound was
5 crystallized from ethanol; m.p. 220 °C. Analysis for $\text{C}_{28}\text{H}_{37}\text{N}_4\text{O}_5\text{S} \cdot 2 \text{HCl}$: Calcd. : C, 53.08; H, 6.20; N, 8.84. Found: C, 52.87; H, 6.15; N, 8.86.

Proceeding as in Example 1, but replacing 1-(3-chloropropane-1-sulfonyl)-4-(4-fluorophenyl)piperazine with other alkyl halides, and then correspondingly as in Example 1, the following compounds of Formula I were prepared:

10 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(morpholine-4-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 192-195 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide; m.p. 160-163 °C;

15 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, dihydrochloride salt; m.p. 186-189 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-ethylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide; dihydrochloride salt; m.p. 220-224 °C;

20 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-propylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, dihydrochloride salt; m.p. 243-245 °C;

25 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-isopropylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, dihydrochloride salt; m.p. 233-236 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-isobutylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, dihydrochloride salt; m.p. 270-271 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-cyclopentyl-piperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, dihydrochloride salt; m.p. 245-246 °C;

5 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-pyrimidin-2-ylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide; m.p. 173-177 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-acetylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 204-208°C;

10 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(furan-2-carbonyl)-piperazine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 148-150 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(tetrahydropyran-4-carbonyl)piperazine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 250-251 °C;

15 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(pyridine-3-carbonyl)piperazine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, dihydrochloride salt; m.p. indefinite;

20 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methanesulfonyl-piperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 236 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(isopropane-2-sulfonyl)piperazine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 165-170 °C;

25 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(4-fluorobenzene-sulfonyl)piperazine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 185-186 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(pyrrolidine-1-sulfonyl)piperazine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 181-182 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(piperidine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 165-168°C;

5 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4,4-dimethyl-piperidine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 108 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(8-azaspiro[4.5]-decane-8-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 160-165 °C;

10 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-propylpiperidine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 125 °C;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methoxy-piperidine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. indefinite;

15 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-carboxamido-piperidine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, hydrochloride salt; m.p. 177-180 °C;

20 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(methanesulfonyl-amino-methyl)piperidine-1-sulfonyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 121-123 °C; and

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[methyl-(1-methylpiperidin-4-yl)sulfamoyl]propyl} piperidin-4-ylmethyl) amide, hydrochloride salt; m.p. 218-219 °C.

EXAMPLE 2

25 2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(piperazine-1-sulfonyl)-propyl] piperidin-4-ylmethyl} amide

The following is the preparation of a compound of Formula Ia wherein R¹, R², R³, and R⁴ are each independently hydrogen, m is 3, and Y is -SO₂.

A mixture of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (piperidin-4-ylmethyl) amide (28.6 g, 104 mmol), 4-(3-chloropropane-1-sulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester (33.9 g, 104 mmol), sodium iodide (7.8 g, 52 mmol), and triethylamine (29 mL, 209 mmol) in *N,N*-dimethylformamide (70 mL) was stirred at 90 °C for 4 hours. The cooled reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water (three times) and brine, dried (Na₂SO₄) and the solvents evaporated *in vacuo*. The crude product was purified by silica gel chromatography (5% methanol-dichloromethane) and crystallization from ethyl acetate-hexane to give 4-[3-(4-([2,3-dihydrobenzo[1,4]dioxin-5-carbonyl)amino]-methyl) piperidin-1-yl)propane-1-sulfonyl]piperazine-1-carboxylic acid *tert*-butyl ester (37.5 g, 64%); m.p. 130-132 °C. Analysis for C₂₇H₄₃N₄O₇ S: Calcd. : C, 57.12; H, 7.63; N, 9.87. Found: C, 57.01; H, 7.40; N, 9.94.

A solution of 4-[3-(4-([2,3-dihydrobenzo[1,4]dioxin-5-carbonyl)amino]-methyl) piperidin-1-yl)propane-1-sulfonyl]piperazine-1-carboxylic acid *tert*-butyl ester (5.7 g, 10 mmol) in dichloromethane (20 mL) was treated with trifluoroacetic acid (8 mL) and the resulting solution was stirred at room temperature for 1 hour. Copious amounts of gas were evolved. The mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and brine, and the aqueous layer was made basic by addition of aqueous ammonium hydroxide solution. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined dichloromethane extract was dried (Na₂SO₄) and evaporated *in vacuo*. The residue was dissolved in ethanol (50 mL) and the solution was made acidic with ethanolic hydrochloric acid. Crystallization was induced by addition of a small amount of ether. Filtration gave the dihydrochloride salt of the title compound (5.1 g, 93%); m.p. 92-94 °C.

EXAMPLE 3

2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-3-(piperazine-1-sulfonyl)-propyl} piperidin-4-ylmethyl}amide

The following is an alternative preparation of a compound of Formula Ia wherein R¹, R², R³, and R⁴ are each independently hydrogen, m is 3, and Y is -SO₂.

A stirred solution of the 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (pyridin-4-ylmethyl)amide (1.30 g, 4.8 mmol) and 4-(3-iodopropane-1-sulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester (prepared from the corresponding chloro compound by treatment with sodium iodide in actone) (2.12 g, 5.1 mmol) in acetonitrile (25 mL) was heated under reflux for 8 hours. The mixture was concentrated *in vacuo* and the residue was triturated with ethyl acetate. Filtration gave the crude pyridinium iodide which was dissolved in methanol (25 mL) and water (5 mL), and hydrogenated over platinum(IV) oxide (450 mg) at atmospheric pressure for 16 hours. The mixture was filtered through Celite® and the filtrate was partitioned between dichloromethane and aqueous ammonium hydroxide. The dichloromethane was dried (Na₂SO₄) and evaporated *in vacuo*. Purification of the residue by silica gel chromatography gave 4-[3-(4-{[2,3-dihydrobenzo[1,4]dioxin-5-carbonyl)amino]methyl} pyridin-1-yl) propane-1-sulfonyl]piperazine-1-carboxylic acid *tert*-butyl ester (1.05 g, 39%).

The 4-[3-(4-{[2,3-dihydrobenzo[1,4]dioxin-5-carbonyl)amino]methyl} pyridin-1-yl) propane-1-sulfonyl]piperazine-1-carboxylic acid *tert*-butyl ester was treated with trifluoroacetic acid as described in Example 2 to give the title compound which was identical to the material prepared in Example 2.

EXAMPLE 4

2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(propane-1-sulfonyl)-piperazine-1-sulfonyl]propyl}piperidin-4-ylmethyl) amide

The following is the preparation of a compound of Formula Ib wherein R¹, R², R³, and R⁴ are each independently hydrogen, R⁶ is propane-1-sulfonyl, m is 3, and Y is -SO₂.

To a 0 °C solution of the 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(piperazine-1-sulfonyl)-propyl] piperidin-4-ylmethyl} amide dihydrochloride (378 g, 0.7 mmol) and triethylamine (233 mg, 2.3 mmol) in dichloromethane (10 mL) was added 1-propanesulfonyl chloride (110 mg, 0.8 mmol). The mixture was stirred for 2 hours with warming to room temperature, diluted with dichloromethane, and washed with saturated aqueous sodium bicarbonate and brine. The dichloromethane extract was dried (Na₂SO₄) and

evaporated *in vacuo*. Purification by silica gel chromatography (7% methanol-dichloromethane) gave the title compound (the free base) as a white solid (167 mg, 42%). The hydrochloride salt was crystallized from ethanolic-hydrochloric acid by addition of ether; m.p. 201-202 °C. Analysis for $C_{25}H_{40}N_4O_7 \cdot S_2 \cdot HCl \cdot 0.3 H_2O$:
5 Calcd.: C, 48.86; H, 6.82; N, 9.12. Found: C, 48.87; H, 6.67; N, 9.04.

EXAMPLE 5

2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide

10 The following is an alternative preparation of a compound of Formula Ib wherein R^1 , R^2 , R^3 , and R^4 are each independently hydrogen, R^6 is methyl, m is 3, and Y is $-SO_2$.

A mixture of the 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-piperazine-1-sulfonyl)-propyl] piperidin-4-ylmethyl} amide dihydrochloride (25 g, 46 mmol) and 10% palladium on carbon (2.2 g) in 50% ethanol-water (200 mL) and 37% aqueous formaldehyde solution (25 mL) was acidified by
15 addition of several drops of hydrochloric acid and then stirred under an atmosphere of hydrogen at room temperature for 12 hours. The catalyst was removed by filtration through Celite® and the filtrate was concentrated *in vacuo*. The residue was partitioned between aqueous ammonium hydroxide and
20 dichloromethane, and the dichloromethane was dried (Na_2SO_4), evaporated, and crystallized from ethanol to give the title compound (free base) as a white crystalline solid (20.8 g); m.p. 163.5-164.5 °C. Analysis for $C_{23}H_{36}N_4O_5S$: Calcd.: C, 57.48; H, 7.55; N, 11.66. Found: C, 57.59; H, 7.58; N, 11.66.

25 The free base was dissolved in ethanol and ethanolic-hydrochloric acid was added until the solution was strongly acidic (pH paper). The resultant precipitate was filtered and washed with ether to give the dichloride salt of the title compound (22.2 g, 87%); m.p. 186-189 °C.

Analysis for $C_{23}H_{36}N_4O_5S \cdot 2 HCl \cdot 0.25 H_2O$: Calcd.: C, 49.50; H, 6.95; N, 10.04. Found: C, 49.41; H, 6.93; N, 10.03.

Proceeding as described above in Example 5, but replacing 2,3-dihydrobenzo-[1,4]dioxine-5-carboxylic acid {1-[3-piperazine-1-sulfonyl)-propyl] piperidin-4-ylmethyl} amide dihydrochloride with 7-chloro-2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(piperazine-1-sulfonyl) propyl] piperidin-4-ylmethyl} amide; and utilizing 10% palladium on carbon with Raney nickel as the hydrogenation catalyst, the following compound of Formula I was prepared:

7-chloro-2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide, dichloride salt; m.p. 223-225 °C. Analysis for $C_{23}H_{35}ClN_4O_5S \cdot 2 HCl \cdot 0.35 H_2O$: Calcd.: C, 46.48; H, 6.39; N, 9.43. Found: C, 46.48; H, 6.29; N, 9.39.

EXAMPLE 6

2,3-Dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide

The following is the alternative preparation of a compound of Formula Ib wherein R^1 , R^2 , R^3 , and R^4 are each independently hydrogen, R^6 is methyl, m is 3, and Y is $-SO_2$.

A mixture of 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (piperidin-4-ylmethyl) amide hydrochloride (2.0 g), potassium bromide (0.95 g), *tetra-n*-butylammonium bromide (0.165 g), trisodium phosphate dodecahydrate (6.03 g), water (6 mL), 1-(3-chloropropane-1-sulfonyl)-4-methylpiperazine (1.69 g), and toluene (28 mL) was refluxed for 21 hours. While still warm the top organic layer was separated, diluted with toluene (13.6 mL), partially concentrated by distillation, and cooled. The crystals were filtered, washed with toluene, and dried to give the title compound (2.82 g, 92%); m.p. 161-162 °C.

EXAMPLE 7

1-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)-3-{1-[3-(morpholine-4-sulfonyl)propyl]-piperidin-4-yl} propan-1-one

The following is the preparation of a compound of Formula Ic wherein R^1 and R^2 are each independently hydrogen, m is 3, Y is $-SO_2$, and Z is morpholino.

A mixture of 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-3-pyridin-4-yl-propan-1-one (500 mg, 1.86 mmol), 4-(3-chloropropane-1-sulfonyl)morpholine (500 mg, 2.23 mmol) and potassium iodide (20 mg) in acetonitrile (12 mL) was heated under reflux for 16 hours. The reaction mixture was concentrated *in vacuo*. The residual crude pyridinium salt was dissolved in N,N-dimethylformamide (10 mL) and hydrogenated over platinum (IV) oxide (100 mg) at atmospheric pressure for 3 hours. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was partitioned between dichloromethane and aqueous ammonium hydroxide and the organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. Purification by silica gel chromatography and followed by treatment with ethanolic-hydrochloric acid and ether gave the hydrochloride salt of the title compound (560 mg, 60%); m.p. 173-175 °C. Analysis for C₂₃H₃₅N₂O₆S·HCl: Calcd. : C, 55.92; H, 7.01; N, 5.57. Found: C, 55.14; H, 7.05; N, 5.72.

EXAMPLE 8

15

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

The ingredients are mixed and dispensed into capsules containing 100 mg each; one capsule would approximate a total daily dosage.

EXAMPLE 9

20

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%

Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidone)	1.0%

The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

5

EXAMPLE 10**Composition for Oral Administration**

Ingredient	<u>Amount</u>
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g

Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

The ingredients are mixed to form a suspension for oral administration.

EXAMPLE 11

Parenteral Formulation (IV)

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection to	100 ml

5

The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

10

EXAMPLE 12

Suppository Formulation

Ingredient	% wt./wt.
Active ingredient	1.0%
Polyethylene glycol 1000	74.5%

Polyethylene glycol 4000	24.5%
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The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

EXAMPLE 13

Topical Formulation

5

Ingredients	grams
Active compound	0.2-2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. 100

All of the ingredients, except water, are combined and heated to about 60°C with stirring. A sufficient quantity of water at about 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. about 100 g.

EXAMPLE 14

Nasal Spray Formulations

Several aqueous suspensions containing from 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 hours.

EXAMPLE 15Thoracic Esophagus 5-HT₄ Receptor Assay

The following describes an *in vitro* assay which utilizes rat isolated esophageal muscularis mucosae to identify test compounds which are 5-HT₄ receptor antagonists.

Thoracic esophagi are isolated from male Sprague-Dawley rats and placed in Tyrode's solution. The outer striated muscle is removed to reveal the muscularis mucosae ("mm"). Each mm is suspended vertically in a 10 mL tissue bath containing methylsergide (1 μ M), cocaine (30 μ M), and corticosterone (30 μ M) in Tyrode's solution maintained at 37 °C, and constantly aerated with a 95% oxygen and 5% carbon dioxide gas mixture.

A resting tension of 1 g is applied to each tissue and thereafter 0.5 g tension is reapplied at 15 minute intervals. A steady state contraction to carbachol (3 μ M) is produced, and then the tissue is exposed to 5-HT in a cumulative-concentration fashion, increasing in concentration until maximal or near maximal relaxation is achieved. The 5-HT produces a concentration-dependent 5-HT₄ mediated relaxation of the mm.

The tissue is exposed to agonist-free Tyrode's solution for 30 minutes and then again contracted with carbachol. The tissue is then exposed to the test compound. If the test compound does not itself elicit relaxation of the mm, the tissue is exposed to 5-HT in the presence of the test compound. Compounds

which inhibit the relaxation responses to 5-HT are characterized as 5-HT₄ receptor antagonists.

Proceeding as in Example 15, the compounds of the present invention were found to be 5-HT₄ receptor antagonists.

5 The Thoracic Esophagus 5-HT₄ receptor assay data

Compound	Affinity pKB (Rat Oesophagus)	Comments
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl]piperidin-4-ylmethyl}amide	8,95	no agonism 1mM
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl]piperidin-4-ylpropyl}amide	9,17	no agonism 1mM

EXAMPLE 16

Pig Tachycardia Assay

10 The following describes an *in vivo* assay for determining the inhibitory effects of compounds of this invention on 5-HT-induced heart rate increases in anesthetized and vagotomized Yucatan micropigs.

15 The animals were surgically prepared prior to conducting the experiments. Briefly, Yucatan micropigs were chemically restrained, anesthetized, intubated with a cuffed endotracheal tube, and ventilated with room air under positive pressure. Needle electrodes were placed subcutaneously to record a limb lead II electrocardiogram, and the right femoral artery and vein were isolated by blunt dissection. In the intravenous study, two polyethylene cannulae were inserted into

the femoral vein, the first for infusion of sodium pentobarbital to maintain a stable plane of anesthesia, and the second for administration of 5-HT and test compound. In the intraduodenal study, a partial midline laparotomy was performed and a polyethylene cannula was inserted into the duodenum for administration of the test compound. The aortic blood pressure and heart rate were measured, and periodic withdrawals of blood samples were performed for blood gas analyses and for determination of plasma compound level. Following a cervical midline incision, both vagus nerves were exposed and severed to abolish vagally-mediated parasympathetic influences on the heart rate. The body temperature was monitored and body heat was maintained. Heparinized saline (50 units heparin sodium per ml) was used to maintain the patency of each vascular cannula throughout the experiment.

Following the surgical preparation, each animal was allowed to equilibrate and stabilize for at least 20 minutes before beginning an experiment. Ascending doses of 5-HT at full-log intervals (0.3-300 $\mu\text{g/kg}$, iv) were administered at 5 to 15 minute intervals to each animal (followed by a 2 mL saline flush) to construct a 5-HT dose-response curve in which responses were expressed as change in heart rate from baseline. A dose that induced a 50% of maximal increase in heart rate (ED_{50}) was graphically selected and repeated in triplicate at 5 to 10 minute intervals to determine a control (pre-dose) response.

In an intravenous dose-response study following the final control period, multiple intravenous doses of the test compound were administered cumulatively at half-log intervals with approximately 30 minute intervals between each dose. A 2 mL saline flush was given after each dose. Each animal was subsequently challenged intravenously with its respective 5-HT ED_{50} dose at 5 and 15 minutes after each dose of the test compound.

In an intraduodenal dose-response study following the final control period, multiple intraduodenal doses of the test compound were administered cumulatively at half-log intervals with a 60 minute interval between each dose. A 3 mL saline flush was given after each dose. Each animal was subsequently challenged intravenously with its respective 5-HT ED_{50} dose at 15, 30, and 45 minutes after each dose of the test compound.

In an intraduodenal duration study following the final control period, a single dose of the test compound which generally produced approximately 70%

inhibition of 5-HT-induced heart rate increases in the intraduodenal dose-response study, or vehicle (deionized water, 0.5 ml/kg) was administered. A 3 mL saline flush was given after each dose. Each animal was subsequently challenged intravenously with its respective 5-HT ED₅₀ dose at 15, 30, 45, and 60 minute post dose and at 30 minute intervals thereafter for the duration of the 6 hour experiment.

Proceeding as in Example 16, the compounds of the present invention were found to be inhibitors of 5-HT induced tachycardia.

INHIBITORY EFFECTS OF 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl]piperidin-4-ylmethyl}amide ON 5-HT-INDUCED HEART RATE INCREASES IN ANESTHETIZED, VAGOTOMIZED YUCATAN MICROPIGS

Compound	N	Route	Dose ^a (μg/kg)	ID ₅₀ ^b	T _{1/2} (min)
Example No. 1 and 5	5	iv	0.03-100	1.15 (1.05-1.25)	--
	4	id	3-1000	51.99 (27.30-76.68)	--
2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl]piperidin-4-ylmethyl}amide	4	id	100	--	>>6 hr

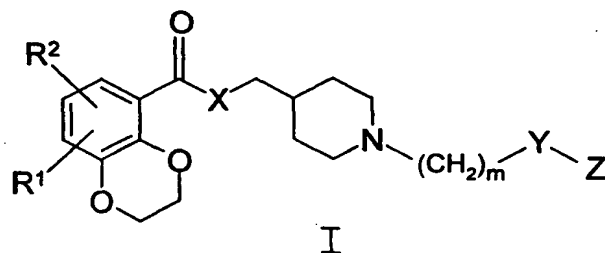
^a Doses in half-log intervals for dose-response experiments; single dose administered in duration experiments.

^b Mean Estimates in $\mu\text{g/kg}$ with 95% Confidence Intervals in parentheses below; ID_{50}s derived from Seemingly Unrelated Nonlinear Regression (SUNR) analyses.

5 While the present invention has been described with reference to the specific
embodiments thereof, it should be understood by those skilled in the art that
various changes may be made and equivalents may be substituted without
departing from the true spirit and scope of the invention. In addition, many
modifications may be made to adapt a particular situation, material, composition
10 of matter, process, process step or steps, to the objective spirit and scope of the
present invention. All such modifications are intended to be within the scope of
the claims appended hereto.

Claims

1. A compound of formula



5 wherein:

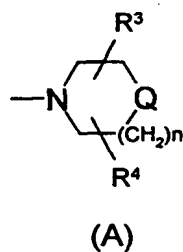
R^1 and R^2 are each independently in each occurrence hydrogen,
(C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, halogen, amino or hydroxy;

X is -NH or -CH₂;

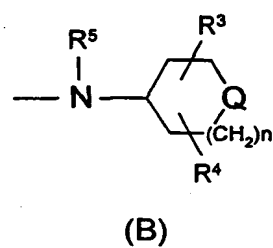
m is 2, 3, or 4;

10 Y is -SO₂;

Z is represented by formula (A) or (B):



or



wherein:

R^3 , R^4 , and R^5 are each independently in each occurrence hydrogen or
(C_1 - C_6)alkyl;

Q is O, S, $-NR^6$, or $-CR^7R^8$;

n is 1 or 2;

5 wherein:

R^6 is hydrogen, (C_1 - C_6)alkyl, (C_3 - C_8)cycloalkyl, heterocyclyl, heteroaryl,
 $-COR^9$, $-SO_2R^9$, $-CONR^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, or aryl optionally mono-
or di-substituted with halogen or (C_1 - C_6)alkyl;

R^7 is hydrogen or (C_1 - C_6)alkyl;

10 R^8 is hydrogen, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, aryloxy, $-(CH_2)_pCONR^{10}R^{11}$,
 $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^7COR^9$, or $-(CH_2)_pNR^7SO_2R^9$; or

R^7 and R^8 taken together with the common ring carbon to which they are
attached form a monocyclic saturated 5- or 6-membered ring
optionally independently containing 0 or 1 heteroatom of nitrogen,
15 oxygen, or sulfur;

wherein:

p is 0, 1, 2, 3 or 4;

R^9 is (C_1 - C_6)alkyl, heteroaryl, heterocyclyl, or aryl optionally mono- or
di-substituted with halogen or (C_1 - C_6)alkyl; and

20 R^{10} and R^{11} are each independently hydrogen or (C_1 - C_6)alkyl;

as an individual isomer, racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or hydrate thereof.

2. The compound of Claim 1 wherein R^1 and R^2 are each independently hydrogen.

5 3. The compound of Claim 2 wherein Y is $-SO_2$ and m is 3.

4. The compound of Claim 3 wherein X is $-NH$.

5. The compound of Claim 4 wherein Z is formula (A), n is 1, and R^3 and R^4 are each independently hydrogen.

6. The compound of Claim 5 wherein Q is $-NR^6$.

10 7. The compound of Claim 6 wherein R^6 is (C_1-C_6) alkyl or (C_3-C_8) cycloalkyl.

8. The compound of Claim 7 wherein R^6 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or cyclopentyl.

9. The compound of Claim 8 wherein R^6 is methyl.

15 10. The compound of Claim 6 wherein R^6 is aryl optionally mono- or di-substituted with halogen or (C_1-C_6) alkyl, or $-SO_2R^9$.

11. The compound of Claim 10 wherein R^6 and R^9 are each independently phenyl, 4-fluorophenyl, or 4-chlorophenyl.

12. The compound of Claim 5 wherein Q is $-CR^7R^8$.

20 13. The compound of Claim 12 wherein R^7 and R^8 are each independently hydrogen or (C_1-C_6) alkyl.

14. The compound of Claim 13 wherein R^7 and R^8 are each independently hydrogen, methyl, ethyl, or propyl.

25 15. The compound of Claim 12 wherein R^7 and R^8 taken together with the common ring carbon to which they are attached form a monocyclic saturated 5- or 6-membered ring optionally independently containing 0, or 1 heteroatom of nitrogen, oxygen, or sulfur.

16. The compound of Claim 15 wherein R⁷ and R⁸ taken together with the common ring carbon to which they are attached form a monocyclic saturated 5-membered ring containing 0 heteroatoms.

17. The compound of Claim 3 wherein X is -CH₂.

5 18. The compound of Claim 17 wherein Z is formula (A), n is 1, and R³ and R⁴ are each independently hydrogen.

19. The compound of Claim 18 wherein Q is O.

20. The compound of Claim 1 which is

10 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-methylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-propylpiperidine-1-sulfonyl)propyl]piperidin-4-ylmethyl} amide;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-propylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

15 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(4-fluorophenyl)piperazine-1-sulfonyl]-propyl}piperidin-4-ylmethyl) amide;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-isopropylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

20 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-cyclopentylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(8-azaspiro[4.5]decane-8-sulfonyl)propyl]piperidin-4-ylmethyl} amide;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid (1-{3-[4-(4-fluorobenzenesulfonyl)piperazine-1-sulfonyl]propyl}piperidin-4-ylmethyl) amide;

25 2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-isobutylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide;

2,3-dihydrobenzo[1,4]dioxine-5-carboxylic acid {1-[3-(4-ethylpiperazine-1-sulfonyl)propyl] piperidin-4-ylmethyl} amide; and

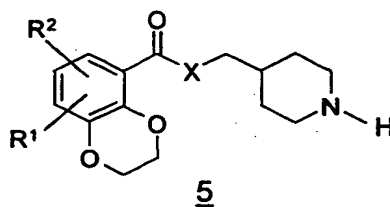
1-(2,3-dihydrobenzo[1,4]dioxin-5-yl) 3-{1-[3-(morpholine-4-sulfonyl)-propyl] piperidin-4-yl} propan-1-one.

21. The pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Claim 1 in admixture with one or more suitable carriers for the treatment of diseases.

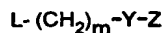
22. The pharmaceutical composition of Claim 21 wherein the compound or compounds are suitable for administration to a subject having a disorder that is alleviated by treatment with a 5-HT₄ receptor antagonist.

23. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



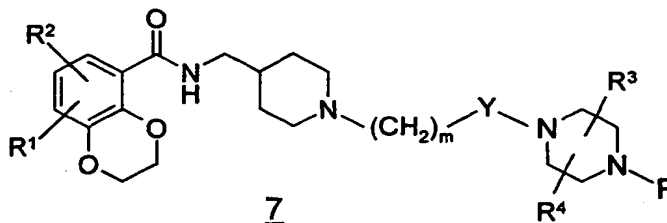
with a compound of formula



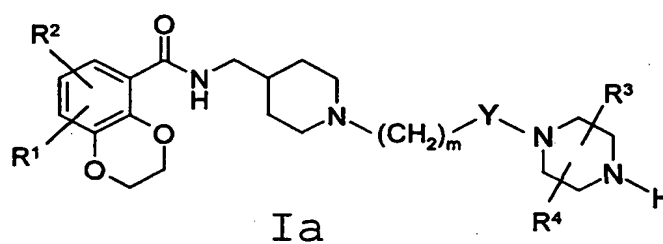
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to a compound of formula I,
wherein the substituents are described above, or

b) deprotecting a compound of formula



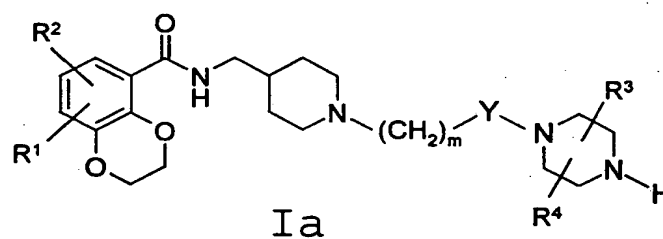
to a compound of formula



wherein the substituents are described above and P is a suitable protecting group,

or

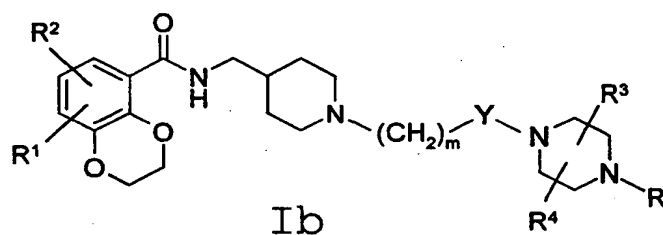
- 5 c) alkylating a compound of formula



with an alkylating agent of formula



to a compound of formula



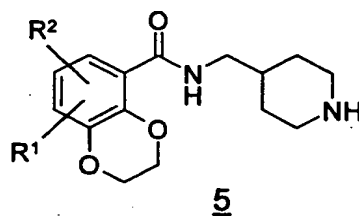
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wherein the substituents are described above and R^6 is other than hydrogen and L is a leaving group,

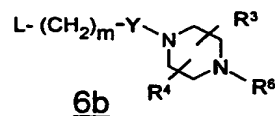
or

- d) reacting a compound of formula

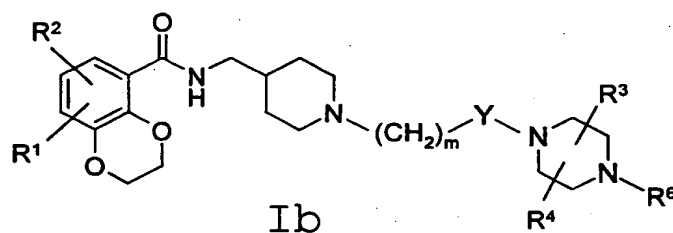
- 73 -



with a compound of formula



to a compound of formula

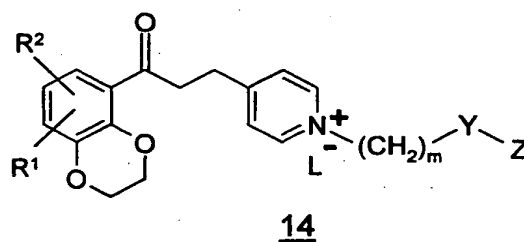


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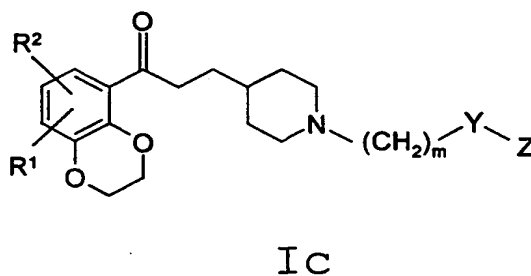
wherein the substituents are described above,

or

e) reducing a compound of formula



10 to a compound of formula



wherein the substituents are given above,

f) modifying one or more substituents within the definitions given above, and,
if desired, converting the compound obtained into a individual isomer or into a
pharmaceutically acceptable salt or hydrate thereof.

5 24. A compound according to any one of claims 1-20 whenever prepared by a
process as claimed in claim 10 or by an equivalent method.

25. The use of compound in accordance with any one of claims 1-20 for the
treatment or prophylaxis of diseases caused by 5-HT₄ receptor antagonistic activity
or for the manufacture of a medicament containing such compound.

10 26. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06402

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/14 C07D413/14 A61K31/445 A61K31/495 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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	-/--	

☒ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- "&" document member of the same patent family

Date of the actual completion of the international search

30 November 1999

Date of mailing of the international search report

07/12/1999

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Herz, C

INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/EP 99/06402

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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